

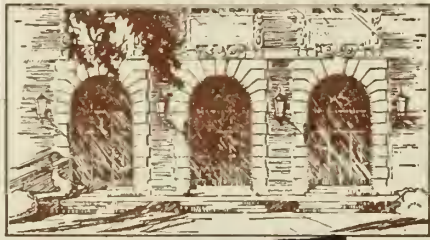
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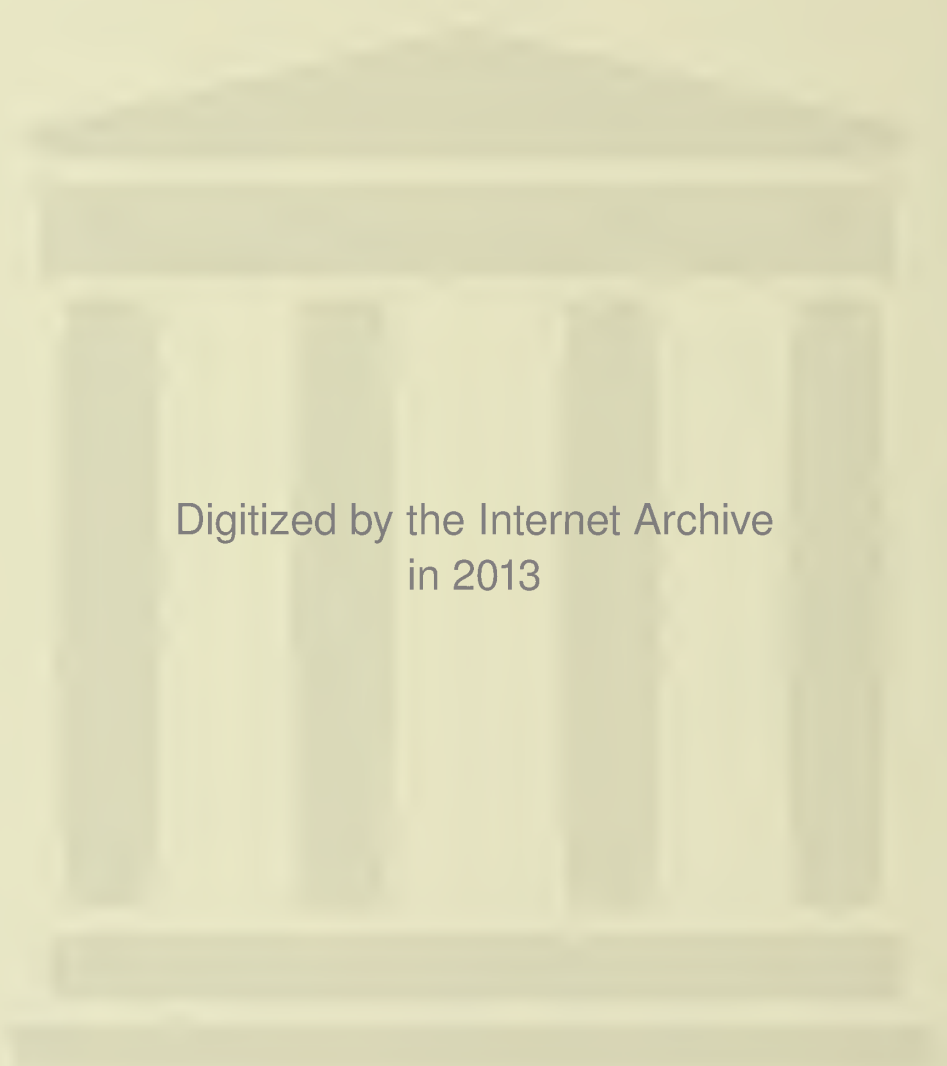
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National Cancer Institute

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CARCINOGENESIS ABSTRACTS

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National Cancer Institute

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

Carcinogenesis Abstracts is normally published monthly. Volume XII covers the scientific literature published from Jan 1974 through Dec 1974. To increase the usefulness of *Carcinogenesis Abstracts*, Volume XII, a Wiswesser Line Notation index and a Chemical Abstracts Service Registry Number index have been provided. These indexes reference compounds described in abstracted articles. A cumulative subject, author, CAS Registry Number, and Wiswesser Line Notation index for Volume XII will be published shortly after the final regular issue.

Carcinogenesis Abstracts is available free of charge to libraries and to individuals who have a professional interest in carcinogenesis. Requests for *Carcinogenesis Abstracts* from qualified individuals should include statements of their relationship to carcinogenesis research. All correspondence should be addressed as follows.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
Ind.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	Rev.	review (only in citations)
i.m.	intramuscular	RNA	ribonucleic acid
i.p.	intraperitoneal	s.c.	subcutaneous
IU	international unit(s)	sec	second(s)
i.v.	intravenous	U	unit(s)
kg	kilogram(s)	UV	ultraviolet
LD ₅₀	median lethal dose(s)	WBC	white blood cells (leukocytes), white blood count
m	meter(s)	wk	week
M	molar	wt	weight
mEq	milliequivalent(s)	yr	year(s)
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		

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- 0001 A NEW CONCEPT OF IMMUNOREGULATION AND ITS APPLICATION TO LEUKEMIA AND LYMPHOMA. (E.) Schwartz, R. S. (Clin. Immunol. Serv., New England Med. Ctr. Hosps., Boston, Mass.). *Tumori* 59:383-386, 1973.

Graft versus host reactions are easily induced by the administration of spleen cells from inbred mice to their F₁ hybrids. Acute graft versus host reactions occur in infant or X-irradiated recipients and are rapidly fatal. Very chronic graft versus host reactions develop when mature recipients are used, and these animals often develop malignant lymphomas. At least three conditions must be met for the induction of lymphomas by foreign lymphoid cells: a strong histocompatibility difference must exist between the donor and recipient; the donor cells must be capable of responding to the histocompatibility antigens of the recipient; and the recipient provides an unidentified factor, which is unrelated to its histocompatibility make-up, and which strongly influences susceptibility to lymphoma induction. Latent murine leukemia viruses (MLV) are activated within 1 week of the induction of the graft versus host reaction. Attempts to identify activated MLV in several other kinds of immune responses were negative. Derepression of the oncogene could lead to the assembly of RNA oncogenic viruses, which appear to exist in all cells and which might then transform the cells to a malignant state. When immunoregulation by antibody is inefficient or defective, widespread derepression of lymphocytes occurs, thereby increasing the possibilities of activating the oncogene. Thus, the lymphocytes have the potential for releasing oncogenic viruses any time their transformation by antigen is poorly regulated. Individuals unable to effectively regulate their immune responses to some kinds of antigens may be liable to the development of malignant lymphoproliferative diseases. Thus, instead of permitting antigenic neoplastic cells to take root, the effect of immunosuppression may be to permit excessive derepression of virus-harboring lymphocytes. (8 references)

- 0002 IMMUNOLOGIC DEFICIENCY IN HODGKIN'S DISEASE. (E.) Sokal, J. E. (Dept. Med., Roswell Pk. Mem. Inst., Buffalo, N.Y.). *Tumori* 59:343-350, 1973.

Hodgkin's disease is characterized by a selective immunologic defect, progressive loss of cellular immune responses, and the production of antibodies at normal or near-normal levels. The cellular immune defect of Hodgkin's disease is demonstrable quite early in the course of the disease, and it becomes more severe as the disease progresses. The severity of the defect may fluctuate considerably according to the activity of the disease; patients are almost uniformly unreactive during active, progressing Hodgkin's disease, but tend to regain delayed hypersensitivity responses after remission is induced. Patients with quiescent disease tend to respond normally to BCG vaccination or DNCB sensitization, while patients with active disease are unresponsive. The lymphocytes of Hodgkin's disease patients also show defective reactivity which varies

with the activity of the disease. Patients with disseminated Hodgkin's disease are unusually susceptible to infections such as fungal and parasitic infections which require cellular immune mechanisms for their control; they are also unusually susceptible to the viral disease, varicella-zoster. They show no excess morbidity or mortality from infectious agents normally controlled by antibody mechanisms. There is a good correlation between immunologic reactivity and survival among Hodgkin's disease patients, indicating that immunotherapy, as with BCG vaccination, may prove useful in the treatment of the disease. (16 references)

- 0003 REPAIR MECHANISMS IN MAMMALIAN CELLS. (E.) Lohman, P. H. M. (Med. Biol. Lab.-TNO, Rijswijk, The Netherlands) and D. Bootsma. *Mutat Res* 23(1):147-150, 1974.

Repair mechanisms in mammalian cells were discussed at an international workshop held in the Netherlands in May 1973. Three general mechanisms for DNA repair have been recognized: excision repair, photoreactivation, and post-replication repair. In order to follow the removal of lesions from the DNA, the lesions must be known, formed in quantities which are detectable with available techniques, and stable towards isolation procedures. Despite the fact that few lesions meet these criteria, evidence for the removal of DNA lesions has been obtained in various mammalian cells following the induction of lesions by chemicals, X-rays, and U.V. irradiation. Evidence of the "by-passing" of DNA lesions has been obtained in microorganisms and some mammalian cells. Three clinically distinct human disease entities associated with defects in DNA repair were described: the two major forms of Xeroderma pigmentosum (XP), and the progeria syndrome. XP and progeria cell lines are among the few well defined examples of mammalian cells lacking at least a part of a DNA repair mechanism and they constitute ideal models for investigating the relationship between defective DNA repair and carcinogenesis or aging. Ligase and a number of endo- and exonucleases, DNA polymerases, and polynucleotide kinase have been identified as possible participants in DNA repair in higher organisms, although the relationship between these enzyme activities and DNA repair and mutagenesis and carcinogenesis is assumed, the causal relationship between DNA repair (or misrepair) and chromosome damage is far from being understood. (No references)

- 0004 TALC DUST AND ITS TOXICITY. (E.) Rajhans, G. S. (Occupational Hlth. Protection Br., Ontario Ministry Hlth, Toronto, Canada). *Can Mining Metallurgical Bull* 67(744):117-118, 1974.

The continued inhalation of significant amounts of talc dust can produce a special kind of pneumoconiosis generally referred to as talcosis. Talcosis appears as a fine diffuse pulmonary fibrosis similar to asbestosis in appearance. The signs and symptoms are those common to other pneumoconioses, e.g., diminished breath sounds, basilar crepita-

tions, limited chest expansion, dyspnea, and cough. Chronic bronchitis and emphysema are frequently associated with this disease. Of all of the varieties of talc dust, the fibrous form (tremolite and asbestine) is probably the most hazardous. The granular variety (steatite) could produce symptomatic pneumoconiosis also providing there was exposure to significant levels. The American Conference of Governmental Hygienists proposes a threshold limit value (TLV) of 20 mppcf for the granular variety and 5 fibers/ml greater than 5 μ m in length for talc containing fibers. The TLVs are determined from data obtained using the impinger and membrane filter techniques, both of which involve relatively short-time samples. In order to obtain representative samples of workers' exposure, however, it is necessary to collect samples under varying conditions and then compare them with the TLVs. (20 references)

0005 BLADDER CANCER AND CARCINOGENIC IMPURITIES IN RUBBER ADDITIVES. (E.) Munn, A. (ICI Ltd., Organics Div., Great Britain). *Rubber Ind* 9(1):19-20, 1974.

In 1949, it was reported that there was an abnormal incidence of papilloma of the bladder among rubber workers and that the responsible agent appeared to be the antioxidant known as 'Nonox S.' Nonox S was manufactured by a condensation reaction of paraldehyde with mixed alpha- and beta-naphthylamines; it contained about 2.5% unreacted naphthylamine, of which 2.25% was the alpha isomer and 0.05% was the beta isomer. Further investigation revealed that occupational cases do not make a major contribution to the frequency of bladder cancer and that there is no evidence that exposure to phenyl-beta-naphthylamine is associated with a bladder cancer hazard. Thus, exposure in industrial conditions to products containing impurities of carcinogenic amines up to 50 ppm appears to constitute a safe dose. Nonetheless, since 1953, National Insurance benefits have been awarded to British workmen who have worked with alpha- or beta-naphthylamine or 'Nonox S' and who have subsequently developed papilloma of the bladder. It must be determined whether it is reasonable to regard exposure to a chemical which is not itself carcinogenic, but which contains trace impurities of a carcinogenic amine, as constituting employment involving exposure to that carcinogenic amine. (11 references)

0006 THE CELL SURFACE IN CELL INTERACTIONS. (E.) Turner, R. S. (Dept. Biochem., Bioctr. U. Basel, Switzerland) and M. M. Burger. *Ergeb Physiol* 68:121-155, 1973.

The role of the cell surface in cell interactions is reviewed. Two types of cell interactions which are widely studied as model systems are considered: the reaggregation of dissociated cells *in vitro*, particularly the reaggregation of dissociated sponge cells; and the density-dependent inhibition of growth of cells in culture. The first system

serves as a model for the first main category of cell interaction - cellular recognition. The second system serves as a model for the second main category - the regulation of cellular activity. At present, enough is known of the reaggregation of sponge cells and density-dependent inhibition of growth of tissue-culture cells to guide future research on these two systems towards the molecular level, the understanding of which is the goal of the experimental analysis of cell interaction. (252 references)

0007 THE BIOLOGICAL SIGNIFICANCE OF TUMOR-BOUND IMMUNOGLOBULINS. (E.) Witz, I. P. (Dept. Microbiol., Tel Aviv U., Israel). *Curr Top Microbiol* 61:151-171, 1973.

The biological significance of tumor-bound immunoglobulins is discussed in terms of: the indications that antitumor antibodies are absorbed *in vivo* by tumor cells; evidence for the *in vivo* coating of tumor cells by Ig; the subclasses of tumor-bound Ig; the spontaneous *in vitro* dissociation of Ig from *in vivo* coated tumor cells; the biological activities of tumor eluates; the nonimmunological binding of immunoglobulins to tumor cells; and the degradation of immunoglobulins by lysosomal enzymes from tumors. The coating of tumor cells with immunoglobulin may result in the following: a complete or partial blocking of the antigenic determinants on the cell surface; the release of complexes between antigens of the cell surface and the corresponding antibodies into the circulation and the possible induction of complete or partial paralysis to the tumor antigens mediated by such complexes; or a temporary decrease or disappearance of cell-surface antigens (antigenic modulation). These situations and their consequences are discussed. (87 references)

0008 PANCREATIC CARCINOMA. A REVIEW OF ETIOLOGIC CONSIDERATIONS. (E.) Mainz, D. (Med. Coll. Georgia, Augusta) and P. D. Webster, III. *Am J Dig Dis* 19(5):459-464, 1974.

Several epidemiologic observations concerning pancreatic carcinoma are well established. The disease is increasing in incidence and, despite improved diagnostic methods, the outcome is usually fatal. Several etiological observations may be drawn from current research. The potential of chemical carcinogens for influencing development of pancreatic carcinoma in animals has been amply demonstrated. The increased incidence of the disease among humans exposed to certain industrial chemicals including methylnitrosourea, acetaminofluorene, paradimethylaminoazobenzene, methylcholanthrene, benznaphthylamine and benznidine has been noted. The incidence of pancreatic carcinoma is 2.5 times more frequent and occurs 10 yr earlier in smokers than in non-smokers. Carbohydrate intolerance is present in about 50% of the patients with pancreatic carcinoma which is a common form of malignancy in diabetics. It is suggested that patients with diabetes mellitus

and calcific pancreatitis may have an increased incidence of pancreatic carcinoma. There is as yet no evidence that bacterial, fungal, or viral agents cause pancreatic cancer in humans. Oncogenic viruses have caused pancreatic sarcomas in animals. A relation between alcoholism and pancreatic carcinoma has not been firmly established. There seems to be no connection between carcinoma of the pancreas and gallstone disease. (46 references)

0009 CHEMICAL CARCINOGENESIS: A LONG-NEGLECTED FIELD BLOSSOMS. (E.) Maugh, II., T. H. (No affiliation). *Science* 183(4128):940-944, 1974.

It is estimated that 60-90% of the 655,000 cases of cancer to be discovered this year in the United States will be caused by environmental factors, mostly chemicals. A recent shift from screening and identifying carcinogens to the study of the chemical interaction between the carcinogen and the cell has shown that most carcinogens must be activated by the host's metabolism. Thus tentative identification of various groups in the population which may be more susceptible to exposure is possible. The development of cell culture systems in which healthy cells may be transformed to malignant ones has been of great significance. Since the biochemical characteristics distinguishing malignant from healthy cells are largely unknown, the ultimate criterion is the formation of a tumor when the cells are injected into a genetically identical animal or one that has undergone immunosuppression. A principle requirement of chemical carcinogens is that they must react irreversibly with cellular macromolecules such as DNA, RNA, or protein to initiate transformation. It is now proposed that the form of the chemical which ultimately reacts with cellular macromolecules must contain a reactive electrophilic center which can attack the many electron-rich centers in polynucleotides and proteins. All carcinogens which are not themselves electrophiles are thought to metabolize to electrophilic derivatives which are the ultimate carcinogens. It is felt that all ultimate carcinogens are also mutagens and with the exception of only 2 classes; all mutagens are generally considered to be carcinogenic. A connection has been made between vitamin A deficiency and the reaction between benzo(a)pyrene and DNA. This is significant in that vitamin A deficiency is common. There is little conclusive evidence to support either a genetic or an epigenetic mechanism of tumor development during the latent period between application of the carcinogen and appearance of the tumor. (No references)

0010 HEPATOMA - NATURE'S MODEL TUMOR. A REVIEW. (E.) Becker, F. F. (New York U. Sch. Med., New York). *Am J Pathol* 74(1):179-200, 1974.

Etiological factors in primary hepatocellular carcinoma include the study of chemically induced

hepatomas in animals; geographical differences in tumor incidence; associations between certain diseases, particularly alcoholic cirrhosis and chronic liver diseases in which the patient is positive for HB Ag; and possible genetic determinants. Of 210 specific cases, the most common pathological form of hepatoma was a major tumor mass (65%), usually of the right lobe and frequently having satellite nodules. The most common gross finding associated with either the massive or multinodular tumor type was tumor penetration into the venous system. Along the spread to the lungs, local nodes and a significant number of vertebral and adrenal metastases were noted. Histologically, these cases ranged from those with a remarkable resemblance to normal liver to some which were totally anaplastic. No etiological association based upon pathological analysis has been made. In the relation between the tumor and the host, some experimental hepatomas have an intense avidity for selected amino acids, thus thwarting all efforts to maintain a normal protein synthesis. The presence or production of a "toxohormone" has been offered to explain the detrimental effects suffered by the host. A sustained elevation of alpha-fetoprotein in an adult is almost invariably associated with hepatoma. Diagnosis usually aims for early detection and definitive analysis, but differentiation of hepatoma from other tumors or from a cirrhotic liver is not easy. Life expectancy of hepatoma patients ranges from 1/2 to 1 yr from onset of symptoms and from 3 to 6 months after diagnosis. Early nodal and vascular spread occurs as evidenced by the frequent and widespread metastases occurring shortly after total surgical removal of the primary hepatoma. Although unsuccessful at the moment, ligation of the exact branch of the hepatic artery which acts as the vascular supply of the tumor offers some hope. (94 references)

0011 DISPUTES ON THE SAFETY OF ASBESTOS. (E.) Wagner, C. (Med. Res. Council, Penarth, Wales). *New Scientist* 61(888):606-609, 1974.

As asbestos usage increased, so did the awareness of hazards to those exposed to the airborne dust. In 1900 a post-mortem performed on an asbestos worker indicated he died of scarring of the lungs, unrelated to tuberculosis. Similar cases occurred and in 1928 investigation revealed 28% of the asbestos workers in the textile industry had pulmonary fibrosis "asbestosis". In 1947, 14% of all deaths in which asbestosis was mentioned, the death was recorded as due to cancer of the lung. By 1969 this figure was over 60% and the incidence of carcinoma of the lung was 10 times that expected among the asbestos workers. By 1957, 16 cases of the rare tumor, mesothelioma, were diagnosed; by 1961 this number rose to 85. Epidemiological studies showed these cases occurred in persons who had been associated with blue asbestos (crocidolite). These tumors were associated with dust exposure, but did not necessarily have severe pulmonary scarring of the lungs. The exposure necessary for mesotheliomas to develop need only

be a few months. In some cases, people born on the Cape in South Africa, where this type of asbestos was originally found, developed these tumors in their 50's and 60's even though they had moved from the area as children. Why this blue asbestos is able to cause this otherwise rare tumor is not known. There is some thought that the physical form of the fiber is important. The blue asbestos has a fine needle-like shape. Experiments have shown that, irrespective of the mineralogical nature of the substance, all fibers less than 0.5 microns in diameter may produce tumors if inoculated into the pleural cavity of rats. Thus manufacturers are warned that health risks increase as fiber diameter is reduced. (No references)

0012 PROTEINS OF POLYOMA VIRUS AND SV40. (E.) Crawford, L. V. (Imperial Cancer Res. Fund. London, England). *Br Med Bull* 29(3):253-258, 1973.

Several properties of polyoma virus and the closely related simian virus 40 (SV40), above all their small size, have made them popular model tumor viruses. The virus particles are about 45 nm in diameter and each particle contains a molecule of double-stranded DNA with a molecular wt of about 3.4×10^6 daltons, i.e., each contains 5500 base pairs. They are thus among the smallest DNA-containing viruses; only the parvoviruses, which contain single-stranded DNA, are smaller. The small size of the genome means that these viruses should be simple, both in structure and in their interaction with cells, because of their restricted coding potential. The basic virus proteins are histones, and the histones VP4, VP5, and VP6 are similar for the two viruses. These proteins are coded for by the host, and they occur only in DNA-containing particles. The remaining virus proteins, VP1 and VP2 (and VP3 for polyoma), seem likely to be virus coded in that they appear in cells only after infection. Proof of their being virus coded would be the *in vitro* synthesis of each protein under the direction of viral DNA of known purity. In both polyoma virus and SV40, there seem to be two groups of mutants which can complement each other, exert their effects late, and reduce the temperature stability of progeny virus particles. This is consistent with a particle's containing at least two virus-coded proteins. The small number of stably transformed DNA virus cells may be related to failure to complete late functions. (40 references)

0013 STUDIES OF CHICKEN SARCOMA (STRAIN 13). A REVIEW. (E.) Stubbs, E. L. (Sch. Vet. Med., U. Pennsylvania, Philadelphia) and A. M. Wallbank. *Poult Sci* 52:2135-2138, 1973.

Chicken sarcoma (strain 13) virus preserved by desiccation from the frozen state and reactivated 20 years later, was restudied by intramuscular injections into the breast muscle, and by i.v. injection into the wing vein of chicks. Following intramuscular injections, tumors appeared at the site of

injection in the breast, followed by tumors in the spleen, liver, gonads, and kidneys. After wing-vein injection, tumors appeared in the wing-vein, spleen, liver, kidney, gonads, and bone marrow. Gross and microscopic changes were the same as reported 20 years earlier. Attempts to produce resistance by introduction of the virus into the vent, by vent drop and vent brush methods, and into the bursa of Fabricius, failed. Chicks at the age of 3 weeks were more susceptible than younger or older chicks. Female chicks showed a higher number of tumors than males. The virus was sensitive to ether and chloroform. The virus remained stable at pH 6.0 through pH 9.0. Contact of the virus with the enzymes trypsin, lipase and hyaluronidase, showed no effect on its ability to produce tumors when injected in chickens. Young guinea fowl developed tumors when injected with the virus. (14 references)

0014 THE LYMPHOID SYSTEM: ABNORMALITIES IN IMMUNODEFICIENCY AND MALIGNANCY. (E.)

Kersey, J. H. (Dept. Lab. Med., U. Minnesota, Minneapolis), K. J. Gajl-Peczalska and M. E. Nesbit. *J Pediatr* 84(6):789-796, 1974.

Infants and young children have a lower percentage but higher absolute number of T cells per cubic millimeter than adults. The percentage and absolute number per cubic millimeter of B lymphocytes was higher in newborn infants than in older children. By reviewing the current knowledge of the lymphoid subpopulations in respect to their occurrence and relationship in immunodeficiency states and malignancy in childhood, several factors were noted. The data indicated that malignancies involving lymphoid subpopulations are very age-dependent. Childhood lymphoid leukemias are most often acute and involve T cells; adult lymphoid leukemias are most often chronic and involve B cells. It is suggested that chronic lymphatic leukemias of older individuals may be chemically induced, whereas acute lymphatic leukemias of childhood may be due to viral agents. A small percentage of normal human lymphocytes carry surface markers characteristic of both T and B lymphocytes. Cells with detectable surface markers are not identified in all cases of acute lymphoblastic leukemia in children. It has been determined that the risk of development of malignancy in individuals with primary immunodeficiency syndromes is about 100 times that of the general population. A better understanding of the pathogenesis of lymphoid malignancies should evolve from studies of the mechanisms controlling proliferation and differentiation of lymphoid cells. (68 references)

0015 CARCINOGENS ARE MUTAGENS: THEIR DETECTION AND CLASSIFICATION. (E.) Ames, B. N. (Biochem. Dept., U. California, Berkeley). *Environ Health Perspect* (6):115-118, 1973.

A set of tester strains of *Salmonella typhimurium* has been developed for detecting mutagens. The principle of the tester strains involves the use

or mutants caused by a known type of DNA damage (base-pair substitutions and the various kinds of frameshift mutations) for detecting mutagens by the highly sensitive and convenient back mutation test. This bacterial test system offers several advantages in the detection of mutagens: small genome; large number of organisms exposed; the positive selection of the mutated organisms; a lack of excision repair; loss of the lipopolysaccharide barrier; and the scoring of mutations in "hot spots" for frameshift mutagenesis. A variety of simple alkylating agents and radiation which are known to be both carcinogenic and mutagenic can be detected with this tester strain, as can a large variety of chemical carcinogens. It has been used to show that epoxides of the carcinogenic polycyclic hydrocarbons are extremely potent frameshift mutagens of the reactive type and that the nitroso metabolites of a variety of aromatic amine carcinogens are very potent frameshift mutagens. A mitochondria-free preparation from rat or human liver can be spread on Petri plates with the tester bacteria to test the variety of metabolites that are made by the microsomal system from a putative carcinogen or mutagen. Work with the tester bacteria has indicated that carcinogens cause cancer because of their action as mutagens. Thus, a simple bacterial test can be used to determine whether a compound is likely to be carcinogenic for humans. (9 references)

0016 THE ROLE OF REPAIR IN ENVIRONMENTAL MUTAGENESIS. (E.) Flamm, W. G. (Food Drug Admin., Washington, D.C.). *Environ Health Perspect* (6):215-220, 1973.

Ultraviolet-sensitive mutants of *E. coli* B₈₋₁ were isolated which were used to show that the excision of pyrimidine dimers from DNA could be correlated with the ability of the cells to recover from the effects of ultraviolet irradiation; these repair-defective mutants were also more sensitive to certain chemical agents than wild-type strains. The repair of ultraviolet damage occurred by a process referred to as excision-repair or repair synthesis. Other types of genetic repair include photoreactivation and recombinational repair, the latter possibly also providing a means of dealing with genetic lesions. Repair synthesis is responsible for the repair of lethal damage and does not lead to mutation, while repair-recombination facilitates and mediates mutagenesis. Specific inhibition or interference with repair processes might lead to reduced cell survival with fewer mutations, reduced cell survival with more mutations, or normal cell survival with fewer mutations. The hereditary disease in humans known as xeroderma pigmentosum is presently the only proven example of a repair-deficient mutant among mammals. There are four ways in which repair synthesis can be assessed in mammalian systems, all of which have in common the need to exclude the normal conservative replication of DNA from consideration when assessing the repair synthesis of DNA. One of these methods, the hydroxyurea approach, is currently being used as an indirect means of

assessing genomic damage among human lymphocytes *in vitro*, particularly with chemical carcinogens and procarcinogens; the approach could also be applied to promutagens. (44 references)

0017 CLINICAL SYNDROMES ASSOCIATED WITH EB VIRUS INFECTION. (E.) Evans, A. S. (Yale U. Sch. Med., New Haven, Conn.). *Adv Intern Med* 18:77-92, 1973.

Evidence indicates that Epstein-Barr virus (EBV) is the cause of infectious mononucleosis (IM), the occurrence of which is inversely related to the age at which the infection occurs. The incidence of clinical IM is related to the number of persons who lack EBV antibody on entering older childhood and young adult life. After maternal antibody disappears, active EBV infection starts; infection with the virus is worldwide, with the prevalence of EBV antibody varying according to the level of socioeconomic development. IM shows a low level of contagiousness, and epidemiological evidence indicates that it is transmitted by intimate oral contact. The clinical aspects of IM are discussed, as is its diagnosis and prevention. A second primary infection with EBV is transfusion mononucleosis, which occurs following the transfusion of EBV antibody-free persons with EBV-positive blood. Other primary host responses include pharyngitis/tonsillitis and asymptomatic infection. Among the chronic diseases associated with EBV is Burkitt's lymphoma, a lymphoma of the jaw in African children. The tumor is endemic in Africa and New Guinea, occurring only sporadically in temperate climates. Evidence implicates EBV as a causal factor in Burkitt's lymphoma, with malaria having been postulated as an important cofactor. Other chronic diseases associated with EBV are nasopharyngeal cancer, Hodgkin's disease, sarcoidosis, and systemic lupus erythematosus. It has been hypothesized that IM is a primary infection with EBV in an immunologically-competent host; the chronic disease syndromes associated with EBV are regarded as a secondary or delayed host responses to EBV infection in immunologically incompetent hosts. At present, there is little experimental support for this hypothesis. (56 references)

0018 PLUTONIUM: BIOMEDICAL RESEARCH. (E.) Bair, W. J. (Biol. Dept., Battelle's Pacific Northwest Labs., Richland, Wash.) and R. C. Thompson. *Science* 183(4126):715-722, 1974.

Plutonium will figure prominently in the production of power during the next several decades. The history of biomedical research on plutonium is reviewed, as are its major chemical and physical properties. Plutonium has found its way to man in readily measurable quantities only through occupational exposure, where the route is usually direct - by ingestion, inhalation, or by way of a plutonium-contaminated wound. The information available on the environmental distribution and

redistribution of plutonium is inadequate for predicting its probable accumulation in man. The distribution, retention, and dosimetry of plutonium in man and other animals is discussed in terms of the lung and pulmonary lymph nodes, wound-sites and regional lymph nodes, the liver, bone, other tissues, and excretion. No specific physical injury to man has been shown to be caused by plutonium exposure; animal studies must be relied upon for all information on the biological effects of the element. The acute toxicity of injected plutonium is due primarily to destructive effects on the hematopoietic system, with osteosarcoma being the most sensitive effect of plutonium injection. The most sensitive manifestation of inhaled PuO_2 is lung cancer. The tissue affected by the neoplastic process will depend on the route of entry and the form of plutonium involved. Countermeasures for internally deposited plutonium include: the surgical removal of tissues adjacent to contaminated wounds; the administration of the chelating agent, diethylenetriaminepentaacetic acid; and pulmonary lavage. An internationally accepted permissible body burden of 40 nanocuries was accepted in 1949, but evidence indicates that permissible exposure limits should be, and within the next few years will be, lowered. More information is needed on the behavior of plutonium in man and his environment. (45 references)

0019 ASBESTOS AND ITS ENVIRONMENTAL IMPACT. (E.) Horvitz, J. S. (U. Connecticut, Storrs). *Environ Affairs* 3(1):145-165, 1974.

There is a definite relationship between exposure to asbestos and diseases such as asbestosis, lung cancer, gastrointestinal cancer, and mesothelioma. It is estimated that at least 2310 asbestos related deaths occur each year in the United States. The legal and regulatory measures which have been taken to reduce the health hazards associated with asbestos exposure are reviewed with reference to the Occupational Safety and Health Act, the Clean Air Act, standards regulating the presence of asbestos in food, drinks, and drugs, and the pollution of water by asbestos. The legal and regulatory response to the environmentally deleterious effects of asbestos contamination have been inadequate, and there is a current need to promulgate strict laws and regulations to curbe the ubiquitous use of these fibers. There is also a need for more complete medical studies relating asbestos exposure to various disease processes. (69 references)

0020 LEUKEMIA AND THE SOMATIC RISKS OF CHEMICAL MUTAGENS. (E.) Lewis, E. B. (Div. Biol., California Inst. Technol., Pasadena). *Environ Health Perspect* 6:185-190, 1973.

The chief biological risks associated with exposure to chemical mutagens are likely to be the induction of mutations in germ cells and of cancers in somatic cells. Serious consideration should be given to the

initiation of a program of prompt monitoring and analysis of leukemia deaths on a national scale. The primary purpose of such a program would be to detect any sudden changes in leukemia mortality rates that might be due to environmental agents. The program would also be able to point up annual trends in already recognized associations and to identify new associations that may have already existed but were previously unrecognized. The program would concentrate on leukemia because: the acute form of the disease has an extremely short latent period; leukemia tends to be more accurately diagnosed and reported on death records than other cancers; age-adjusted leukemia death rates in the U. S. white population appear to have largely stabilized; and there is little or no evidence of seasonal variation in the incidence of the disease in the U. S. or of clustering of cases. The basic data would be analysed for time trends in age-specific death rates for each major type of leukemia. (15 references)

0021 DELINEATION OF PERSONS AT EXCEPTIONALLY HIGH RISK OF CANCER. (E.) Miller, R. W. (Natl. Cancer Inst., Bethesda, Md.). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 279-285, 1973.

Insight into the etiology of cancer may be gained by identifying persons at exceptionally high risk of developing specific neoplasms. Among a variety of inborn abnormalities which are associated with specific cancers are chromosomal abnormalities (leukemia), immunological deficiency states (lymphoma), and manifestations of growth excess (Wilms' tumor). Insight into etiology may also be gained by studying familial cancer clusters involving a single cell type or dissimilar cell types; subclinical abnormalities might be found in affected family members as well as certain healthy relatives. Genetics seems to play a role in the etiology of some cancers. When a genetic basis for a certain cancer is suspected, a series of persons with the neoplasms can be evaluated for an excess of consanguineous parentage. In Japan, where 7% of marriages involve cousins, a study revealed there is a consanguinity effect when leukemia occurred in sibs but not when it occurred sporadically. Similarly, monozygotic twins show a much higher concordance rate for childhood leukemia than do dizygotic twins. The induction of cancer may also be related to environmental factors such as occupational exposure to certain chemicals and the use of certain drugs. In addition, the geographic clustering of certain cancer types can provide clues relating to etiology, as can notable deficiencies of specific types of cancer in certain geographic locations. In the future, identification of circumstances that carry a high risk of cancer will be promoted by the establishment of national and international centers for referral of unusual observations made by alert medical practitioners. (31 references)

0022 IMMUNOLOGIC DEFENSES AGAINST CANCER. (E.) Bernstein, I. D. (U. Washington Sch. Med., Seattle). *J Pediatr* 83(6):906-918, 1973.

A variety of clinical observations suggest that host immune responses play a role in the control of neo-

plastic disease. Most tumors studied, whether spontaneous or induced by carcinogens, viruses, or physical agents, have been found to contain tumor-specific transplantation antigens which are not present on normal cells. These antigens may or may not be cross-reacting, are believed to be cell surface components, may be an integral part of the neoplastic process, may be organ or tissue type specific, and may normally be found during embryonic development. *In vitro* assays for the detection of tumor antigens include transplantation and serologic techniques and cell-mediated assays such as lymphocyte transformation and macrophage migration inhibition. The response to tumor antigens can be mediated by both humoral factors and lymphoid cells. Monocytes accumulated at a tumor site in response to an interaction between tumor antigen and lymphocytes may have a significant role *in vivo* in killing tumor cells. Serum in certain cases may act synergistically with certain nonimmune cell types to kill specific tumor cells, although sera from organisms with progressively growing tumors are capable of blocking the action of immune lymphocytes against the appropriate target cells. Reasons why tumors may occur and grow despite the host defensive mechanisms may include: the presence of a blocking factor, insufficient early immune response, inadequate numbers of immune lymphocytes, insufficient effector cells, an impaired immune response, alterations in tumor antigens, and the stimulation of tumor growth by lymphoid cells. Immunologic procedures which may cause rejection of limited amounts of tumor cells might be used following surgery, chemotherapy, and/or radiotherapy. Such procedures might include actively immunizing the patient, passively immunizing the patient, and administering agents such as BCG which can generally heighten the immune response. (103 references)

0023 RISK GROUPS FOR WOMEN WITH RESPECT TO
CERVICAL CARCINOMA MORBIDITY. (Rus.)

Charkviani, L. I. (Sci. Res. Inst. Oncol., Ministry Hlth., Georgian SSR, USSR). *Vopr Onkol* 19(12):91-94, 1973.

Risk factors for cervical cancer are identified on the basis of epidemiological and experimental research. The incidence of cervical cancer in Georgia between 1965 and 1970 was 0.8/100,000 for women below 30 yr old and reached a maximum (88.4/100,000) in the group between 50 and 60 yr old. The incidence of cervical cancer is increased in women who reach sexual maturity at age 16 yr or after age 16 yr, who enter menopause before age 40 yr or after 50 yr, who discontinue breast feeding early or fail to lactate, and who have vitamin deficiencies. Other factors increasing the incidence of cervical cancer include frequent abortions, early or late pregnancies and births, smegma, trichomoniliasis, and cervical precancers (hyperplasia, hypertrophy, leukoplakia, polyps, pseudoerosion). The risk is particularly high in women with cervical precancer combined with the other risk factors. (14 references)

0024 POLYVIROGENY AND CARCINOGENESIS. (Rus.)

Irlin, I. S. (N. F. Gamaleia Inst. Epidemiol. Microbiol., Moscow, USSR), A. F. Bykovskii and V. M. Zhdanov. *Vopr Virusol* (2):230-235, 1973.

It is postulated that there are groups of viruses called "integrative" viruses with genomes, called virogenes, which are capable of integrating with the cell genome. The virogenes is not a normal component of a normal cell but is a functioning or nonfunctioning genome of a DNA-containing virus or a DNA transcript of an RNA-containing virus integrated into the genome of a normal cell. The term, polyvirogeny, is used to represent a particular form of genetic symbiosis between the virus and cell which can be defined as molecular integrative symbiosis. Different DNA- and RNA-containing oncogenic and nononcogenic viruses can be present in the genome of a normal cell in the form of virogenes. Virogenes of the same viruses, called polyvirogenes, or of different viruses, called polyheterovirogenes, can be incorporated into the same normal cell. Virogenes can be located on one or more chromosomes or in the genetic apparatus of mitochondria, centrioles, etc. This heterogeneous system of virogenes can be found not only in different individuals of populations, but in various normal cells in the same organism. For a virus to occur in the virogenes form it is necessary that: (a) DNA be present in the genetic material of the virus, RNA-containing viruses be in the DNA stage, or a DNA transcript be present; (b) the genome of a DNA-containing virus or the DNA transcript of a RNA-containing virus be capable of integrating with the cell genome; (c) there be repression of the productive cycle of the DNA-containing virus. The virogenes can be present in an inducible or a noninducible form. Viral replication occurs with complete induction; partial synthesis of its components, including a number of virus-specific antigens, occurs with incomplete induction. Tumor transformation is a special case of virogeny in which a transforming gene of an integrated oncogenic virus called the oncogene, functions in the cell. Depending upon whether the site of integration is in germ cells or somatic cells, virogenes can be transmitted vertically by Mendelian laws or by parental laws of heredity. In the first case it is possible for the virogenes to exchange with various virogenes alleles in the offspring; in the second transplacental or horizontal transmission of the virus is possible with complete induction. Induction of a productive cycle in DNA-containing viruses can be accompanied by "eliminating" the virogenes from chromosomes, while for RNA-containing viruses it is sufficient for the virogenes to be transcribed in RNA, since the latter is also a viral genome. Integration of the virogenes from oncogenic viruses and the development of neoplastic processes does not apparently present any real danger to the population of an animal species, since neoplastic processes develop when the oncogene is derepressed and this occurs most often in exposure to radiation or to carcinogens and in ageing of the individual. The first two factors are unnatural and the third has no effect on the fate of a population since neoplasms develop primarily in individuals who have passed the reproductive age. Integration of virogenes from oncogenic viruses might prove useful for the population of a biological species since the presence of the virogenes may protect the cell from invasion by similar pathogenic viruses. Some virogenes can lose their induction ability during ontogenesis or phylogenesis and thereby take on the function of "cell" genes.

The assimilated virogenes can play a role in regeneration and differentiation which are accompanied by reverse, nonmalignant cell transformation. The integration of viral virogenes is a special case of integration processes which are common in prokaryocytes and eukaryocytes. Viruses can be considered to be mediators of genetic exchange in the biosphere and important factors for the evolution of life on earth. (14 references)

0025 MYCOTOXINS: METABOLISM AND LIVER INJURY.

(E.) Patterson, D. S. P. (Central Vet.

Lab., Weybridge, Surrey, U. K.). *Biochem Soc Trans* 1(4):917-922, 1973.

The metabolic fates of the aflatoxins, sterigmatocystin, ochratoxins A and B, and the trichothecene series of mycotoxins are discussed. Aflatoxin B₁ is probably converted to a highly reactive metabolite before causing liver injury. Generally, the rate of metabolism is fastest in species that are highly susceptible to acute aflatoxin poisoning. These species convert aflatoxin B₁ quickly into the 2-hydroxy derivative, the hemiacetal. The hemiacetal binds to proteins, probably forming Schiff bases and possibly causing liver necrosis in a nonspecific manner. Aflatoxin G₁ can also be converted into its hemiacetal in the liver. However, aflatoxins B₂ and G₂ cannot undergo this transformation and are correspondingly less toxic. It is also possible that the carcinogenic properties of aflatoxin may be dependent on its conversion into a 2,3-epoxide, which may exist as a transient intermediate in the liver. The structure of sterigmatocystin is similar to that of aflatoxin, and it can be converted into its hemiacetal by treatment with mineral acid. However, there is no evidence that this transformation takes place in the liver. Ochratoxin A is metabolized slowly in the liver, and there is evidence that its phenolic hydroxyl group is important to its hepatotoxicity. Scirpene triacetate is detoxified by the liver. Unstimulated metabolism does not primarily involve epoxide hydration, whereas phenobarbital pretreatment stimulates this mode of detoxification. (23 references)

0026 THE NATURAL HISTORY OF AUSTRALIA ANTIGEN.

(E.) Blumberg, B. S. (Inst. Cancer Res.,

Fox Chase, Philadelphia, Pa.). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 109-125, 1973.

On the basis of available data relating to the biological properties of the Australia antigen (Au), a model which can be used for the formulation of hypotheses and experiments is proposed. The Au agent is pictured as having antigenic characteristics which may or may not be shared by putative hosts. The degree of matching will determine the results of infection, e.g., persistent infection, acute infection, development of antibody, formation of complex, combinations of these. The antigenic specificities of the host which may or may not match with the Au agent are, at least in part, genetically determined; some of these inherited host antigenic specificities may be reflected in serum protein

polymorphisms, for example the immunoglobulins (Gm). There is little direct information on the action of Au on the cells of the host after infection takes place. Presumably it can enter the cellular mechanism of the host and cause the host to produce additional quantities of Au. The presence of Au in the cells may also have an effect on the cellular immunity of the host. Au can be transmitted from individual to individual by horizontal transmission (simple infection). The nature and pathogenesis of the resulting infection may depend on the route of infection, e.g., through the blood, the gastrointestinal tract. It may also be transmitted vertically, in that there appears to be an inherited susceptibility to persistent infection. In addition there is another form of vertical transmission determined by a maternal effect. This may be manifest in the mother's egg cell although the present data do not rule out the operation of the maternal effect later in the life of the child. Factors in addition to genetic ones, such as sex and age, also have a measurable effect on the transmission of the agent. On the basis of association studies, Au appears to be related to a variety of diseases in addition to hepatitis. It is possible that in some cases this may reflect a pathogenetic role (e.g., in hepatoma) but in others may mean that the agents which cause the disease (e.g., lymphocytic leukemia) have properties in common with Au. These considerations do not, of course, rule out the possibility that an agent more similar to a virus and related to Au, may eventually be identified. (39 references)

0027 ETIOLOGY OF BLADDER CANCER: "METABOLIC"

ASPECTS. (E.) Yoshida, O. (Faculty Med.,

Kyoto U., Japan) and M. Miyakawa. *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 31-39, 1973.

Metabolic studies may play an important role in determining the epidemiology of bladder cancer and could contribute to the prevention of the disease. 2-Naphthylamine, benzidine, chlornaphazine, and 4-aminobiphenyl produce bladder cancer in man, and many other substances have been recognized as bladder carcinogens in experimental animals. For example, bracken fern has clearly demonstrated carcinogenic and leukemogenic activities in animals. However, the fact that in Japan this plant is used in large quantities as human food indicates that conventional methods of testing for carcinogens using experimental animals and obtaining epidemiological information are inadequate with respect to the detection of potential human carcinogens in the environment. 2-Naphthylamine induces bladder tumors in humans, dogs, and monkeys but not in rats and mice. However, metabolic studies indicated that it should be able to induce such tumors in mice. The findings that this chemical did induce bladder tumors in mice whose bladders contained glass beads supported the metabolic studies. It has been found that there is a high incidence of bladder cancer among dyers using benzidine dyes. These dyes contain no free benzidine, but benzidine can be the product of metabolic activity by intestinal flora, *Escherichia coli* and soil bacteria. Thus the large

amounts of dyestuffs in the environment are not always stable and may be a potential public health hazard. (10 references)

0028 VIROLOGICAL AND ENDOCRINOLOGICAL ASPECTS OF CARCINOMA OF THE UTERINE CERVIX. (E.)

Munoz, N. (Inst. Agency Res. Cancer, Lyon, France). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 51-61, 1973.

Epidemiological and experimental evidence indicate an association between herpes simplex virus type 2 (HSV-2) and cervical carcinoma. Epidemiologically, there is good correlation between the epidemiological features of cervical carcinoma and genital herpes. Furthermore, sero-epidemiological studies have shown an association between HSV-2 and cervical carcinoma, and women with herpetic cervicitis have a 2 to 10 times greater risk of developing carcinoma *in situ* than do unaffected women. Experimentally, HSV-2 antigens have been demonstrated in cervical cancer cells, HSV-2 has been isolated from spontaneously degenerating cultures of human cervical carcinoma cells grown *in vitro*, and HSV-2 has proven highly oncogenic in hamsters. The association between HSV-2 and cervical carcinoma could be causal or non-causal. In support of a causal relationship, there is evidence that estrogens have a carcinogenic effect on humans and experimental animals. Hypothetically, HSV-2 could be one of the initial factors which will trigger the neoplastic transformation of susceptible cervical cells, and estrogens and/or other hormones could be some of the promoter factors which will stimulate the subsequent growth of the transformed cells. When this hypothesis was tested experimentally, the data indicated that, in mice, estrogens are more important than HSV-2 in the etiology of cervical carcinoma. Thus, although an association between cervical carcinoma and HSV-2 and/or estrogens appears to exist, the nature of this association is unknown. (43 references)

0029 ECOLOGICAL GENETICS OF RNA TUMOR VIRUSES AND THEIR HOSTS. (E.) Weiss, R. A.

(Imperial Cancer Res. Fund Labs., London, England). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 201-233, 1973.

RNA tumor viruses are endemic in many species of animals. They are transmitted from one host to another via: horizontal infection by contact or proximity; congenital infection from mother to offspring; and genetic transmission from either parent in the form of DNA proviruses integrated into the chromosomes of the gametes. The infectious modes of transmission are subject to host range barriers which are genetically determined by the host. While a single Mendelian gene has an overriding influence on host susceptibility to infection in both mice and chickens, resistance is dominant in mice but recessive in chickens. The ecological genetics of the RNA tumor viruses and their hosts are viewed in relation to the different modes of transmission and host range controls operating in natural populations. The interactions between different kinds of RNA tumor

virus are also viewed in relation to their natural history. None of the various models concerning the natural history of the RNA tumor viruses in animal populations appears to be singularly appropriate to human cancer, although this may reflect differences in the genetic structure of human and animal populations rather than a fundamental difference in the etiology of cancer. (111 references)

0030 NATURAL HISTORY (SEROEPIDEMIOLOGICAL) STUDIES IN THE DELINEATION OF THE VIRAL ONCOGENE HYPOTHESIS. (E.) Huebner, R. J. (Natl. Cancer Inst., Bethesda, Md.). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 345-365, 1973.

According to the viral oncogene hypothesis, most if not all cancers of vertebrates are specified by oncogenes of RNA tumor virus genomes inherited as part of natural DNA component vertebrate cells. Further, defects or breakdowns in the host cell gene regulation of the endogenous oncogenes and virogenes and also of the host's immunological surveillance system represent natural supplementary causes of spontaneous cancers. It appears that the RNA tumor viruses are transmitted primarily in the form of inherited DNA copies in the germinal and somatic cells of all vertebrates and that the inherited oncogenes and virogenes are responsible for the generality of both spontaneous and induced cancers. In support of these hypotheses, considerable epidemiological and experimental evidence indicates that oncogenic information is genetically inherited, that RNA tumor virus genomes are genetically transmitted, and that endogenous RNA viral oncogenes are responsible for cancer. (88 references)

0031 THE SIGNIFICANCE OF NUCLEIC ACID HOMOLOGY STUDIES FOR ETIOLOGY AND EPIDEMIOLOGY OF HUMAN TUMORS. (E.) zur Hausen, H. (Inst. Clinical Virol., The U., Erlangen-Nurnberg, Germany). *Proc Third Int Symposium Princess Takamatsu Cancer Res Fund, Japan* 153-160, 1973.

Nucleic acid homology studies between viral and tumor cell DNAs performed on nitrocellulose filters have been useful in showing the degree to which these DNAs will hybridize. A recent method for measuring the reassociation kinetics of nucleic acids with the aid of hydroxyl-apatite column chromatography provides an accurate estimate of the numbers of viral genome equivalents per tumor cell. Other recent techniques involve the separation of DNA-RNA hybrids according to their differences in buoyant density and the *in situ* hybridization of cytological preparations to allow the localization of specific nucleic acids by autoradiography. Nucleic acid hybridizations are being used with increasing frequency to establish a relationship between certain human malignancies and suspected tumor viruses. For example, nucleic acid hybridization experiments have revealed the presence of Epstein-Barr viral DNA in all established lymphoblastoid cells tested up to now. In contrast, while the herpes simplex type 2 virus has been implicated in the induction of human cervical carcinoma, nucleic acid homology studies do not support a causal rela-

tionship between this virus and cervical carcinoma. Other nucleic acid homology studies have shown that RNAs from human mammary tumors, leukemias, sarcomas, and lymphomas anneal with DNA transcribed from Rauscher murine leukemia virus RNA; these findings support the hypothesis that there may be a close relationship between mouse leukemia agents and hypothetical human leukemia viruses. Nucleic acid hybridizations also represent the only available test system to study the epidemiology of human warts and to establish the relationship between this virus and other proliferations of human tissues. (22 references)

- 0032 CHANGES IN THE CELL SURFACE DURING TUMORIGENESIS. (Rus.) Vasil'ev, Iu. M. (No affiliation). *Zh Vsesoiuz Khim Obschestva im D. I. Mendeleeva* 18(6):621-628, 1973.

After a brief consideration of components normally present in and directly beneath the cell membrane, the author discusses the reaction of receptors on the cell surface with molecular effectors, contact reactions with foreign bodies and the surfaces of other cells, and changes which occur in the ability of the cell surface to react with factors in the environment during tumorigenesis. During tumorigenesis changes occur in the synthesis and location of oligosaccharides on the cell surface, in the activity of adenyl cyclase and the permeability of the cell membrane to sugars. Brief reference is made to research on changes which occur in lipids in the cell membrane and fibrillar structures located under the cell membrane which play an active role in surface movement. (114 references)

- 0033 BRAIN TUMORS. (E.) Zimmerman, H. M. (No affiliation). *Methods Cancer Res* 10:105-128, 1973.

Brain tumors are discussed in terms of tumors produced with higher aromatic hydrocarbons (20-methylcholanthrene, 3,4-benzpyrene, and 1,2,5,6-dibenzanthracene), electron microscopic observations of experimental brain tumors (including materials and methods, the observation of virus particles, and the oncogenicity of virus particles), tumors produced with resorptive carcinogens (methylnitrosourea and ethylnitrosourea), and tumors induced with viruses (Rous sarcoma virus, murine sarcoma virus, and DNA oncogenic viruses). (71 references)

- 0034 INITIAL STAGES OF PLASMACYTOMA. (Ger.) Brucher, H. (Steglitz Clin., Free U., Berlin, Germany). *Blut* 28(2):136-140, 1974. (35 references)

- 0035 ADENOMA OF THE NIPPLES: A REVIEW OF CLINICAL FEATURES AND MORPHOLOGY. (Ger.) Kindermann, G. (Clin. Obstet. Gynecol., U. Erlangen, Germany) and W. Rummel. *Geburtshilfe Frauenheilkd* 33(9):724-728, 1973. (27 references)

- 0036 NEVUS FLAMMEUS AND HEMANGIOMA. (Ger.) Hundeiker, M. (Dermatol. Clin., U. Giessen, Germany) and K. Brehm. *Fortschr Med* 91(20-21):855-856, 1973. (16 references)

- 0037 THE ROLE OF RIBONUCLEOPROTEINS OF LARGE RNA-CONTAINING VIRUSES IN THE INITIATION OF INFECTION. (Rus.) Bukrinskaya, A. G. (D. I. Ivanovskii Inst. Virol., Moscow, USSR). *Vopr Virusol* (1): 3-12, 1973. (54 references)

- 0038 MOLECULAR BIOLOGICAL ASPECTS OF RESEARCH ON ONCOGENIC VIRUSES. (Rus.) Kiselev, F. L. (D. I. Ivanovskii Inst. Virol., Moscow, USSR). *Vopr Virusol* (4):387-396, 1973. (224 references)

- 0039 DEFECTIVE PARTICLES IN A VIRAL POPULATION. (Rus.) Kantorovich, E. N. (D. I. Ivanovskii Inst. Virol., Moscow, USSR). *Vopr Virusol* (3):259-266, 1973. (75 references)

- 0040 CURRENT DATA ABOUT CHANGES IN PROTEIN METABOLISM IN MALIGNANT BLOOD DISEASES. (Rus.) Iavorkovskii, L. I. (No affiliation). *Sov Med* (8): 105-111, 1973. (102 references)

- 0041 METHYLATION OF NUCLEIC ACIDS UNDER NORMAL CONDITIONS AND IN LEUKEMIA. LITERATURE REVIEW AND PERSONAL FINDINGS. (Rus.) Fedorov, N. A. (Ctr. Inst. Hematol. Blood Transfusion, Moscow, USSR). *Probl Gematol Pereliv Krovi* 18(6):50-56, 1973. (69 references)

- 0042 MALIGNANT TUMORS IN THE EAR, NOSE AND THROAT REGION. IV. TUMORS OF THE PAROTID GLAND. (Ger.) Lange, D. (Munic. Clin., Berlin-Buch, Germany) and W. Kup. *Arch Geschwulstforsch* 42(4): 358-371, 1973. (97 references)

- 0043 MEDULLARY CARCINOMA OF THE THYROID. (E.) Corwin, T. R. (Washington U. Sch. Med., St. Louis, Mo.). *Surg Gynecol Obstet* 138(3):453-458, 1974. (28 references)

- 0044 B AND T LYMPHOCYTE SUBCLASSES IN IMMUNODEFICIENCY AND LEUKEMIC DISORDERS IN MAN. (E.) Hadden, J. W. (Dept. Med., Sloan Kettering Inst., New York, N.Y.). *Clin Bull* 3(4):146-149, 1973. (No references)

- 0045 MALIGNANT PELVIC TUMOURS IN INFANCY AND CHILDHOOD. (E.) Ghazali, S. (Inst. Child Hlth., London, England). *Z Kinderchir* 13(3):339-354, 1973. (35 references)

- 0046 ENVIRONMENTAL MUTAGENS. (E.) Bendix, S. (Bendix Res., Berkeley, Calif.). *Science* 184(4133):188-189, 1974. (No references)

- 0047 YIN-YANG HYPOTHESIS OF GROWTH CONTROL. (E.) Hogan, B. (Sch. Biol., U. Sussex, England) and R. Shields. *New Sci* 62(897):323-325, 1974. (No references)
- 0048 EUROPEAN TUMOUR VIROLOGY AT AVIEMORE. (E.) Rogers, E. (No affiliation). *Nature* 249 (5433):112, 1974. (No references)
- 0049 AN ASSESSMENT OF THE DELANEY CLAUSE AFTER 15 YEARS. (E.) Oser, L. B. (Food Drug Res. Labs., Inc., New York, N.Y.). *Food Cosmet Toxicol* 11(6):1121-1138, 1973. (No references)
- 0050 IMMUNOLOGICAL ASPECTS OF CHEMICAL CARCINOGENESIS. (E.) Baldwin, R. W. (Cancer Res. Campaign Labs., U. Nottingham, England). *Adv Cancer Res* 18:1-75, 1973. (33 references)
- 0051 PHYSIOLOGICAL AND BIOCHEMICAL REVIEWS OF SEX DIFFERENCES AND CARCINOGENESIS WITH PARTICULAR REFERENCE TO THE LIVER. (E.) Toh, Y. C. (Sub-Dept. Endocrine Pathol., U. Liverpool, England). *Adv Cancer Res* 18:155-209, 1973. (566 references)
- 0052 IMMUNODEFICIENCY AND CANCER. (E.) Kersey, J. G. (Dept. Pathol., U. Minnesota, Minneapolis), B. D. Spector and R. A. Good. *Adv Cancer Res* 18:211-230, 1973. (160 references)
- 0053 GLYCOLIPIDS OF TUMOR CELL MEMBRANE. (E.) Hakomori, S.-I. (Sch. Public Hlth., U. Washington, Seattle). *Adv Cancer Res* 18:265-315, 1973. (280 references)
- 0054 CHEMICAL ONCOGENESIS IN CULTURE. (E.) Heidelberger, C. (McArdle Lab. Cancer Res., U. Wisconsin, Madison). *Adv Cancer Res* 18:317-366, 1973. (215 references)
- 0055 CARCINOGEN METABOLISM AND HUMAN CANCER. (E.) Conney, A. H. (Hoffmann-La Roche, Inc., Nutley, N.J.). *New Engl J Med* 289(18):971-973, 1973. (15 references)
- 0056 CARCINOMA ARISING IN A DUPLICATED COLON. CASE REPORT AND REVIEW OF THE LITERATURE. (E.) Heiberg, M. L. (Royal Victoria Hosp., Montreal, Canada), K. G. Marshall and H. S. Himal. *Br J Surg* 60(12):981-982, 1974. (5 references)
- 0057 BIOCHEMICAL ASPECTS OF THE SEARCH FOR CARCINOGENIC VIRUSES. (Dut.) Bentvelzen, P. (Radiobiol. Inst., TNO, Rijswijk, Netherlands). *Chem Weekbl* 70(1):13-15, 1974. (24 references)

0058 IRREVERSIBILITY OF THE ALTERATION IN RNA TRANSPORT INDUCED BY AN AZO-DYE CARCINOGEN IN THE RAT LIVER. (E.) Shearer, R. W. (Dept. Molecular Biol., Pacific Northwest Res. Fdn., Seattle, Wash.). *Biochem Biophys Res Commun* 57(3):604-610, 1974.

DNA/RNA hybridization was used to study the mammalian regulatory mechanism which selects only certain RNA species for transport to the cell cytoplasm. The livers of male Buffalo rats fed 3'-methyl-4-dimethylaminoazobenzene (3'MeDAB) incorporated into their diet lost this mechanism within a few days. The mechanism was not repaired within 8 months of the animals being returned to a normal diet. Altered RNA transport also occurred in the livers of adult rats whose parents had been given the carcinogenic diet for 3 weeks ending on the ninth day of gestation. These data indicate that a genetic control mechanism which operates at the translational level can be irreversibly altered by a chemical carcinogen, and that the defect cannot be diluted by subsequent rapid cell proliferation.

0059 BONE TUMOURS IN CF-1 MICE. (E.) Charles, R. T. (Int. Agency Res. Cancer, Lyon, France) and V. S. Turusov. *Lab Anim* 8(2):137-144, 1974.

Benign osteomas occurring late in life in CF-1 mice were observed through six consecutive generations, their average incidence being higher among control females (11.5%), DDT and urethane treated females (17.4%), and DDT and urethane treated males (11.7%) than among control males (8.5%). Multiple affected sites were found in 20% of the mice. The skull was involved in about 90% of the untreated osteoma-bearing mice, the limbs in 12%, the vertebral column in 9%, and the sacrum and pelvis in 3%. In the treated mice, the skull was involved in approximately 80% of the cases, the limbs in 20%, the vertebral column in 12%, and the sacrum and pelvis in 8%. The osteomas affecting the skull were represented by small nodules 2-3 mm in diameter, while those affecting other sites reached a much larger size (6-10 mm or more). Multiple osteomas with many large nodules at various sites were also observed. Fifteen osteosarcomas (10 in females and 5 in males) were found: five in control animals, 9 in DDT-treated animals, and one in a urethane-treated mouse. The primary tumor was found in the limbs (6 mice), vertebral column (5), ribs (2), or mandible (1); nine of these tumors metastasized. There was little evidence of clustering of osteomas, but the number of osteoma-bearing animals per litter was significantly higher if at least one parent also had a tumor.

0060 DO 'HOT' PARTICLES IN TOBACCO CAUSE CANCER? (E.) Anonymous. *New Scientist* 62(899):456, 1974.

Dr. E. Martell of the U.S. National Center for Atmospheric Research has suggested that it is the radioactive particles in cigarette smoke which lead to lung cancer. In the case of cigarettes, the alpha emitter is polonium-210, which is found in tobacco, cigarette smoke, and smokers' lungs. This theory is similar to that first proposed in 1964. Tobacco, cigarette smoke, and smokers' lungs also contain radioactive lead-210, which decays to Po-210. Unlike Po-210, Pb-210 is insoluble and should persist in the lung. Pb-210 decays to Po-210 by double beta decay with a half-life of 21 years, which explains the long delay between smoking and the onset of cancer. Furthermore, insoluble dust accumulations in the bronchi contribute to lymphatic stagnation and thus to a larger accumulation of metabolic products. This could explain why asbestos workers who smoke show an increased likelihood of cancer, while those who do not smoke show no excess.

0061. VARIATIONS OF MITOSIS-INHIBITING CHALONE ACTIVITY IN EPIDERMIS AND DERMIS AFTER CARCINOGEN TREATMENT. (E.) Rohrbach, R. (Dept. Path., U. Freiburg, West Germany) and O. D. Laerum. *Cell Tissue Kinet* 7(3):251-257, 1974.

The mitotic rate was determined in epidermis and dermis from untreated hairless mice and mice treated with methylcholanthrene (MCA) and extracts of normal and MCA-treated dermis and epidermis. During the regeneration and hyperplasia which followed a single application of MCA to the epidermis, the rate of epidermal cell proliferation varied inversely with the level of mitosis-inhibiting activity (chalone). The primary inhibitory activity was present within the epidermal cells, but a lesser activity was also found in the corresponding dermal extracts. When extracts made from MCA-treated epidermis were tested on untreated mouse epidermis, the mitosis-inhibiting activity underwent simultaneous, but not identical, changes. Extracts of MCA-treated dermis also significantly inhibited the mitotic rate in the normal epidermis. Extracts of normal dermis insignificantly lowered the epidermal mitotic rate. These data support the concept that chalones act as physiological regulators of cellular proliferation under pathological as well as normal conditions.

0062 OSHA AND MATERIALS TOXICITY: THE ISSUE GROWS, AND THE IMPACT BEGINS. (E.) Anonymous. *Mod Plastics* 50(8):16, 1973.

Forthcoming Occupational Safety & Health Act toxicity standards may restrict the use of some of the plastics components (fillers, additives, chemicals, monomers) which are currently under OSHA scrutiny. If a plastics component were restricted, alternatives for the manufacturer would be a costly worker-pro-

tection compliance procedure or the exploitation of alternative materials. However, the situation need not be calamitous. For example, the Polyurethane Manufacturer's Association is seeking relief from an OSHA emergency standard which would restrict the use of the allegedly carcinogenic component MOCA (4,4'-methylene(bis)-2-chloroaniline). Some suppliers in the polyurethane field have, however, switched to alternative materials which offer the same performance values as MOCA without its alleged hazards.

0063 THE EFFECT OF BILE ON THE INDUCTION OF EXPERIMENTAL INTESTINAL TUMORS IN RATS.

(E.) Chomchai, C. (Dept. Surg., Wayne St. U., Detroit, Mich.), N. Bhadrachari and N. D. Nigro. *Dis Col Rect* 17(3):310-312, 1974.

The flow of bile was diverted from the proximal half of the small intestine to the distal half in 25 young male Sprague-Dawley rats. Following recovery, half of the rats were given azoxymethane (8 mg/kg) at weekly intervals for 9 months. Ten unoperated rats were given a similar azoxymethane treatment. All of the azoxymethane treated animals developed intestinal tumors, with the rats with the implanted bile ducts developing significantly more tumors (155) than the normal rats (67). None of the operated rats given no azoxymethane developed tumors. All of the tumors in the azoxymethane treated animals were adenocarcinomas. The fecal bile-salt content was higher in the operated animals than in the unoperated animals. Thus, bile salts in the colon appear to have some role in the pathogenesis of intestinal tumors in rats given azoxymethane.

0064 INHIBITORY EFFECT OF SODIUM CYCLAMATE AND SODIUM SACCHARIN ON TUMOR INDUCTION BY 2-ACETYLAMINOFLOURENE IN RATS. (E.)

Ershoff, B. H. (Inst. Nutritional Studies, Culver City, Ca.) and G. S. Bajwa. *Proc Soc Exp Biol Med* 145(4):1293-1297, 1974.

The effects of orally administered sodium cyclamate and sodium saccharin on tumor incidence was studied in 48 female Horton-Sprague-Dawley rats fed the carcinogen 2-acetylaminofluorene (AAF). Of 12 rats fed a natural food stock ration supplemented with 300 mg AAF/kg diet, 11 (91.7%) developed palpable mammary and ear duct tumors during a 40-week period in contrast to a tumor incidence of 2 out of 12 rats (16.7%) fed a similar ration supplemented with 5% sodium cyclamate and 6 of 12 rats (50%) fed a diet containing 5% sodium saccharin. Judging by gross and microscopic examination of the livers of surviving rats after the 40 week period, administration of sodium cyclamate and sodium saccharin also resulted in a marked reduction in the size of liver tumors of rats fed AAF. The mechanism by which sodium cyclamate and sodium saccharin produce these protective effects is not known at the moment.

0065 AFLATOXIN Q₁: A NEWLY IDENTIFIED MAJOR METABOLITE OF AFLATOXIN B₁ IN MONKEY LIVER. (E.) Masri, M. S. (Western Regional Res. Lab., USDA, Berkeley, Calif.), W. F. Haddon, R. E. Lundin and D. P. H. Hsieh. *J Agr Food Chem* 22(3):512-515, 1974.

The conversion of aflatoxin B₁ by rat and monkey liver postmitochondrial preparations to two main metabolites, aflatoxin M₁ and aflatoxin Q₁, has been reported. In this paper, a study of the structure of aflatoxin Q₁ was undertaken. Evidence suggests that aflatoxin Q₁ is an isomer of aflatoxin M₁ with the hydroxyl group on the carbon atom beta to the carbonyl of the cyclopentenone ring. Aflatoxin Q₁ gave a crystalline O-acetyl derivative with acetate anhydride in pyridine. UV spectrum of aflatoxin Q₁ had λ max 366, 267, and 223 nm. IR spectrum was similar to aflatoxin B₁ but had absorption bands at 3460 and 3550 cm⁻¹. Mass spectrum of aflatoxin Q₁ indicated a molecular weight of 328 and an elemental composition of C₁₇H₁₂O₇. The 100-MHz nmr spectrum of aflatoxin Q₁ in dimethylformamide-d-7 was similar to that of aflatoxin B₁ except for signals assigned to protons of the cyclopentenone ring. In liver postmitochondrial fractions of both monkey and rats, the conversion of aflatoxin B₁ to M₁ was about 1-3% of the substrate. The conversion to aflatoxin Q₁ in the rat liver was also about 1-3%, but was much higher, from 19-52%, in the monkey liver, indicating that aflatoxin Q₁ is distinctly a major metabolite in these primates *in vitro* and may also be a major metabolite in other primates, including man.

0066 LUNG CANCER AND SMOKING - THE EVIDENCE REASSESSED. (E.) Rosenblatt, M. (New York Med. Coll., N.Y.). *New Sci* 62(897):332, 1974.

The pattern of sex distribution of lung cancer, which predominantly occurs in males, has not changed since the 19th century when cigarette consumption was relatively insignificant. Thus it is suggested that constitutional, i.e., genetic factors play an important role in susceptibility to the disease. The characteristic occurrence of lung cancer in older age groups, usually in the 5th - 7th decades of life, bears a relation to the increased longevity of the population, in that the incidence of lung cancer thus seen increased. Duration of smoking and age at onset have little influence on the development of lung cancer. Of great importance are the improved methods of diagnosing the disease, thus increasing the number of cases reported. It is suggested that overdiagnosis resulting from use of diagnostic methods which are not definitive, may have accounted for some of the increased incidence of the disease over the past years. The premise that squamous cell cancer results from smoking whereas adenocarcinoma occurs without any known cause, thus explaining the occurrence of lung cancer in non-smokers, is incorrect, for the basic explanation for

different cancer types is embryological. It is noted in conclusion that experimental confirmation of smoking causing lung cancer is lacking.

0067 BILATERAL BREAST CANCER 10 YEARS AFTER AN AUGMENTATION MAMMAPLASTY. (E.)

Johnson, M. (Beverly Hosp., Mass.) and H. E. D. Lloyd. *Plast Reconstr Surg* 53(1):88-90, 1974.

A 47-yr-old female presented with masses in both breasts. A bilateral augmentation mammoplasty had been performed 10 years earlier using Etheron sponge implants, no longer in use at this time. There was no family history of cancer. She had been taking chlorpromazine for anxiety, but no other drugs. Bilateral incisional breast biopsies showed adenocarcinoma. Treatment consisting of 5,000 rads of Cobalt⁶⁰ radiation to each breast and to the regional lymph nodes was begun. After 6 months, treatment with Thiotepe and testosterone was begun at 2 week intervals for 8 months. Back and shoulder pains were noted 6 months later, with shortness of breath following in another 3 months. Prednisone therapy improved the dyspnea. A bilateral oophorectomy offered no improvement. Due to bone marrow involvement a pancytopenia developed. Retinal metastases were found. Death occurred after another 4 months, 1 1/2 yr from the discovery of the disease. Autopsy revealed metastases in the lung, liver, lymph nodes, spleen, thyroid, adrenals, and spine. Microscopic sections of both breasts showed prosthetic material with surrounding fibrous tissue. Areas of carcinoma were present within and around the prosthetic material in both breasts.

0068 EFFECT OF SODIUM NITRITE CONCENTRATION ON THE FORMATION OF NITROSPYRROLIDINE AND DIMETHYLNITROSAMINE IN FRIED BACON. (E.)

Sen, N. P. (Food Res. Labs., Dept. Health Welfare, Ottawa, Canada), J. R. Iyengar, B. A. Donaldson and T. Panalaks. *J Agr Food Chem* 22(3):540-541, 1974.

Fried bacon samples prepared with 0-, 50-, 100-, 150-, and 200-ppm levels of sodium nitrite were analyzed for nitrospyrrolidine and dimethylnitrosamine. Results clearly demonstrated a gradual increase in the levels of nitrospyrrolidine in fried bacon with an increase in the concentration of sodium nitrite used in the preparation of the bacon. Even samples prepared with the lowest level of sodium nitrite added, 50-ppm contained traces (2-4 ppb) of nitrospyrrolidine. Samples with increased levels of sodium nitrite contained traces up to 20 ppb. The levels of nitrospyrrolidine correlated well with the initial concentrations of nitrite but not with that of nitrite found in the raw bacon just prior to frying. No nitrospyrrolidine was found in raw bacon, suggesting that the presence of this compound in fried bacon may result from an intermediate nitroso compound which is probably produced during the early stages of the curing of

bacon and thus its concentration is dependent on the initial concentration of nitrite. The identity of nitrospyrrolidine in a few samples was confirmed by glc-mass spectrometry.

0069 CONTROL OF CATABOLISM OF MITOCHONDRIA IN ONCOGENESIS I. INCREASE OF HEPATIC MITOCHONDRIAL POPULATION DURING FEEDING INACTIVE OR marginally ACTIVE AMINO AZO DYES: ABSENCE OF *DE NOVO* BIOSYNTHESIS. (E.) Wu, B. C. (USPHS Hosp., New Orleans, La.), M. F. Argus and J. C. Arcos. *Chem Biol Interact* 7(6):399-416, 1973.

Administration of 2-methyl-4-dimethylaminoazobenzene (0.06%) and 4-dimethylaminoazobenzene (0.063%) to male Sprague-Dawley rats increased the amount of liver mitochondria by 47% and 31%, resp. This was not due to *de novo* mitochondriogenesis. This increase in mitochondria correlated with an approximately 10% decrease of total liver protein per g of tissue. Mitochondrial ATP synthesis was drastically impaired following feeding of 2-methyl-4-dimethylaminoazobenzene beyond 1 week. Determination of the polysome profile and polysome/monosome ratio at intervals during 2-methyl-4-dimethylaminoazobenzene administration showed no change. During administration of 4-diethylaminoazobenzene however, a small but definite rise of the polysome-monomosome ratio was noted. Administration of 2-methyl-4-dimethylaminoazobenzene up to 42 days drastically inhibited (³H)thymidine incorporation into both DNA's, approximately 59% with mitochondrial DNA and 77% with nuclear DNA, suggesting these templates could not be involved in the substantial increase of the mitochondrial population. These data suggest that the increase results from a steady accumulation due to increase of the half-life of mitochondria, owing perhaps to an inhibition of lysosomal catabolic enzymes.

0070 INDUCED SALIVARY GLAND TUMORS IN PRIMATES. (Rus.) Ordzhonikidze, G. G. (Res. Inst. Oncol., Ministry Hlth. Georgian SSR, USSR). *Soobshch Akad Nauk Gruz SSR* 73(2):485-487, 1974.

A tumor was induced in 1 of 10 rhesus monkeys (*Macaca mullata*) by a single injection of 30 mg dimethylbenzanthracene in a 10% benzene solution into the submaxillary gland. Palpation revealed a tumor measuring 0.5 x 0.5 cm five months after injection; during the next two months the tumor increased in size to 2.0 x 2.5 cm. Gross examination revealed a benign polymorphic adenoma which was characterized by different degrees of proliferation and differentiation. This tumor is considered a satisfactory model for human salivary gland tumors. Histological examinations of the salivary glands in 7 monkeys showed, in addition to regenerative metaplastic changes, proliferative processes in the parenchyma and stroma ranging from diffuse hyperplasia to foci of epithelial proliferation. These examinations were performed after the monkeys died (8 died before 25 months had passed). The remaining 2 monkeys are still under observation.

0071 USE OF MONKEY LIVER MICROSOMES IN PRODUCTION OF AFLATOXIN Q₁. (E.) Hsieh, D. P. H. (Dept. Environ. Toxicol., U. California, Davis), J. I. Dalezios, R. I. Krieger, M. S. Masri and W. F. Haddon. *J Agr Food Chem* 22(3):515-517, 1974.

Aflatoxin Q₁, a newly identified monkey liver metabolite of aflatoxin B₁, was prepared in milligram quantities in the crystalline form by biotransformation of aflatoxin B₁ using monkey liver microsomal preparations. Parameters needed for quantitation of aflatoxin Q₁ using a spectrodensitometer are determined with the aid of radiolabeled metabolites. An amount as small as 1 ng can be measured with certainty. The availability of aflatoxin Q₁ will make possible studies on its chemical properties, toxicity, and possible role in the carcinogenicity of aflatoxin B₁.

0072 ASCORBIC ACID AND BIOLOGICAL ALKYLATING AGENTS. (E.) Edgar, J. A. (CSIRO Div. Animal Health, Parkville, Victoria, Australia). *Nature* 248(5444):136-137, 1974.

Administration of sodium ascorbate, together with an oral dose of dimethylnitrosamine, partly prevented the liver damage produced by dimethylnitrosamine alone, thus demonstrating an ascorbate-mediated protection not involving competition for nitrous acid. A mechanism for this protective effect has been proposed. Under physiological conditions, alkylation of the ascorbic acid anion occurs mainly at C₂ of the ambident nucleophile, producing a new carbon-carbon bond. This bond is not particularly susceptible to hydrolytic cleavage, and thus alkylation of ascorbic acid will effectively compete with the alkylation of other cellular nucleophilic sites such as those on nucleic acids and proteins. This mechanism may account for the protective effect of sodium ascorbate against the hepatotoxicity of dimethylnitrosamine. If present in sufficient amounts, ascorbic acid may also afford protection from the adverse effects of several other environmental alkylating agents by this same mechanism. It is suggested that some of the biological effects of alkylating agents which have in the past been associated with their ability to alkylate nucleophilic sites on nucleic acids and proteins, may stem from the alkylation and rapid depletion of cellular ascorbic acid.

0073 EFFECTS OF DIETARY PHENOBARBITAL ON THE BINDING OF 2-ACETYLAMINOFLOURENE TO RAT LIVER NUCLEAR DNA. (E.) Mushlin, P. S. (Div. Biol. Med. Res., Argonne Natl. Lab., Ill.) and C. Peraino. *Proc Soc Exp Biol Med* 145(3): 859-862, 1974.

A group of 10 male Charles River mice received a nutritionally adequate diet containing 30% casein and an additional 5 mice received the same diet supplemented with 0.05% phenobarbital.

On day 79 each rat received 2-acetylaminofluorene (7.1 mg/kg, i.p.). After 3 days, 5 mice which had not been receiving the phenobarbital supplemented diet were changed to a 0.04% phenobarbital diet. DNA isolated from livers of rats given a single injection of 2-acetylaminofluorene-9¹⁴C contained bound label for at least 9 weeks after injection. When phenobarbital feeding was begun after labeled 2-acetylaminofluorene metabolites had become bound to DNA, no significant reduction in binding occurred despite a 42-62 day exposure to the phenobarbital diet. However, when phenobarbital was fed for 77 days prior to administration of labeled 2-acetylaminofluorene, binding was reduced by approximately 80%. It is suggested that this protective effect of dietary phenobarbital against 2-acetylaminofluorene-induced hepatic tumorigenesis probably results from a reduction in the concentration of 2-acetylaminofluorene metabolites able to bind to key target molecules such as DNA. On the other hand, once such binding occurs, it may be virtually irreversible and the resultant carcinogen-DNA complex may then become subject to phenobarbital-induced metabolic processes which enhance its tumorigenic potential. Caution is urged in using chemoprophylactic agents which, like phenobarbital, may increase the degradation of a carcinogen and substantially reduce the amount able to reach the site of action, but may also cause metabolic changes which increase the risk of tumorigenesis from any remaining carcinogen molecules which escape degradation and bind irreversibly to tumorigenically important target molecules.

0074 SMOKING AND LUNG CANCER: BURCH'S REPLY. (E.) Burch, P. (Dept. Med. Physics, U. Leeds, Great Britain). *New Scientist* 61(887): 559-560, 1974.

While there are many undeniable positive associations between smoking and cancer, the causal hypothesis explaining the association suffers from two weaknesses: it relies heavily on qualitative statements which are unsupported and sometimes contradicted by quantitative evidence; and no mechanism of tobacco carcinogenesis has been proposed which can be tested quantitatively. The claim that the risk of lung cancer is diminished by stopping smoking is not supported by findings that a large increase in recorded death rates accompanied an increase in the proportion of ex-smokers in Britain between 1958 and 1965. Data indicate that recorded increases in lung cancer are attributable not to increased cigarette consumption but to changes in diagnosis. The constitutional hypothesis for the association between smoking and lung cancer is supported by twin studies which show equal death rates among low-smoking and high-smoking members of monozygotic twin pairs. There are also incidences of populations of people who achieve extreme longevity despite a high consumption of cigarettes. Finally, experiments demonstrating the carcinogenic action of tobacco condensates on the skin of mice appear to have little or no relevance to lung cancer in man.

0075 ULTRASTRUCTURE AND PHYSIOLOGICAL EFFECTS OF NONTOBACCO CIGARETTES ON TETRAHYMENA.

(E.) Gray, J. P. (Dept. Zool., U. Tennessee, Knoxville) and J. R. Kennedy. *Arch Environ Health* 28(5):283-291, 1974.

The ciliated protozoan *Tetrahymena pyriformis* was exposed to smoke filtrates from 2 nontobacco, nonnicotine cigarettes, one made of grass and the other of lettuce. Ultrastructural alteration consisted primarily of degradation of the mitochondria, including dissolution of the inner tubular cristae and an infolding of both membranes. After exposure to these residues for 60 min, ciliastasis occurred and oxygen consumption was reduced by more than 90%. The effect of purified nicotine in the amount found in an individual cigarette (0.08 mg/ml) revealed no substantial reduction in oxygen consumption, no ciliastasis, and no loss of ultrastructural integrity. These results indicate that smoke filtrates of any combustion material may produce mitochondrial damage, impairment of oxygen consumption, or ciliastasis.

0076 ARYL HYDROCARBON HYDROXYLASE INDUCTION IN MOUSE PERITONEAL MACROPHAGES AND BLOOD-DERIVED HUMAN MACROPHAGES.

(E.) Ptashne, K. (Stanford U. Sch. Med., Palo Alto, Ca.), L. Brothers, S. G. Axline and S. N. Cohen. *Proc Soc Exp Biol Med* 146(2):585-589, 1974.

When benzantracene was added *in vitro* to 48 hr cell cultures of mouse macrophages (C57B1/6 strain), a 2.25 fold induction of aryl hydrocarbon hydroxylase activity as compared to activity in cells cultured 48 hr without inducer was noted. Cells cultured 96 hr showed a 1.64 fold increase of enzyme activity. When levels of aryl hydrocarbon hydroxylase activity in mouse peritoneal macrophages were compared to enzyme levels in mouse liver, the liver exhibited 70 times more activity. The enzyme levels in mouse liver increased 7 fold when induced *in vivo* with 3-methylcholanthrene. Addition of benzantracene to cultures of blood-derived human macrophages resulted in a 2.73 fold induction of benzopyrene hydroxylase as compared to untreated macrophage cultures. These results demonstrate the presence of benzopyrene hydroxylase activity in human macrophage cultures and provide a system for studying aryl hydrocarbon hydroxylase induction in these cells.

0077 JAPANESE GASTRIC CANCER. POTENTIALLY CARCINOGENIC SILICATES (TALC) FROM RICE.

(E.) Matsudo, H. (St. Joseph Med. Ctr., Burbank, Cal.), N. M. Hodgkin and A. Tanaka. *Arch Pathol* 97(6):366-368, 1974.

Transmission and scanning electron microscopy as well as energy-dispersive x-ray analysis have shown the presence of talc crystals in gastric cancer cells in 6 of 7 Japanese individuals with gastric adenocarcinoma. The presence of crystalline particles containing magnesium and silicon,

presumably talc, on the surface of unwashed Japanese "coated" rice, on the surface of washed and washed-cooked rice and in the wash water from the rice was noted - even after the rice had been washed in 9 completely separate rinses before cooking. As the rice absorbs water and swells to facilitate cooking, the remaining particles become trapped in the grain. No asbestos particles were noted either by light or electron microscopy or by x-ray spectra of the particles discovered. It is suggested that the practice of coating rice with talc, a practice undertaken to improve the appearance and taste, be reconsidered.

0078 THE METABOLISM OF BENZO(a)PYRENE IN RAT LIVER MICROSOMES: THE EFFECT OF ASBESTOS-ASSOCIATED METAL IONS AND pH.

(E.) Thomson, R. (Natl. Res. Inst. Occupational Dis., Johannesburg, South Africa), I. Webster and T. A. Kilroe-Smith. *Environ Res* 7(2):149-157, 1974.

It is hypothesized that trace metals and other factors associated with asbestos mined in different areas play a more critical role in the development of "asbestos tumors" than the actual fiber itself. The effect of these factors on the metabolism of benzo(a)pyrene was studied *in vitro* using rat liver microsomes containing benzpyrene (BP) hydroxylase. The amount of benzo(a)pyrene metabolized by the enzyme in these microsomes was measured in the presence of increasing amounts of trace metal ions. Copper, zinc, lead, nickel, chromium, ferrous, ferric, and magnesium ions inhibited the enzyme activity in a concentration-related fashion. Manganese ions activated the enzyme at lower concentrations and inhibited it at higher concentrations. The enzyme activity was also considerably affected by changes in pH, the activity dropping off considerably at higher pH values. In general, the pH values of suspensions of Cape crocidolite and chrysotile were considerably higher than those of amosite, anthophyllite, and tremolite; a very wide range was found with Transvaal crocidolite. The effect of manganese ions on BP hydroxylase activity differed at various pH values, the enzyme-activating effect of these ions being restricted to a much smaller concentration range at high pH values. Any change in the delicate balance in which all influencing factors must exist for the optimum detoxification of BP may be critical in the development of asbestos-associated cancers.

0079 MODIFICATION OF TOXIC LIVER INJURY IN THE RAT. I. EFFECT OF INHIBITION OF PROTEIN SYNTHESIS ON THE ACTION OF 2-ACETYLAMINOFLUORENE, CARBON TETRACHLORIDE, 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE AND DIETHYLNITROSAMINE.

(E.) Flaks, B. (U. Bristol Med. Sch., Great Britain) and J. W. Nicoll. *Chem Biol Interact* 8(3):135-150, 1974.

Male Leeds and Wistar rats were treated with single doses of varying amounts of diethylnitrosamine (DEN), 2-acetylaminofluorene (2-AAF),

3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB), or carbon tetrachloride (CCl₄), with or without simultaneous single doses of cycloheximide (CHM, 1.5 mg/kg). The rats were killed 24 to 48 hours after treatment and their tissues examined histologically. CHM alone produced no histological changes or liver glycogen depletion. DEN induced congestion, progressive centrilobular necrosis, and liver glycogen depletion in a dose related fashion; high doses caused death. Simultaneous treatment with CHM greatly reduced the necrogenic effects of DEN, but did not prevent the congestion, glycogen depletion, or mortality. All rats treated with 2-AAF, alone or in combination with CHM, showed severe centrilobular or generalized liver depletion. However, CHM prevented the congestion, centrilobular hepatic cell vacuolation, nuclear damage, and necrosis caused by 2-AAF. CHM also prevented the hepatic cell damage caused by 3'-MeDAB, although it did not prevent the depletion of glycogen. The necrogenic effect of the lower doses of CCl₄ was markedly prevented by CHM; CHM appeared to increase the mortality caused by higher doses. These data support the view that protein synthesis may play an important role in the mechanism of cell death, and that it is the inhibition of protein synthesis which protects against the action of hepatotoxic agents.

0080 MUTAGENICITY OF REACTIVE DERIVATIVES OF CARCINOGENIC HYDROCARBONS: EVIDENCE OF DNA REPAIR. (E.) Maher, V. M. (Dept. Biol., Michigan Cancer Fdn., Detroit), D. Douville, T. Tomura and J. L. van Lancker. *Mutat Res* 23(1):113-128, 1974.

7-Bromomethylbenz(a)anthracene (7-BrMeBA) and 7-bromomethyl-12-methylbenz(a)anthracene (7-BrMe-12-MeBA) (0.05-2.0 mM) dissolved in acetone were added to biologically active DNA isolated from two strains of *Bacillus subtilis* (hcr⁺ and hcr⁻) which differ in their ability to repair UV-induced DNA lesions. The hydrocarbons were shown by specific radioactivity to be covalently linked to the DNA at a frequency of from 1-5 per 1000 nucleotides. An increased frequency of bound hydrocarbon molecules was directly correlated with a decrease in the buoyant density of the DNA. The survival of biological activity was higher in the hydrocarbon-bound DNA from the repairing strain of bacteria (hcr⁺) than in the nonrepairing strain. A higher frequency of mutations was also detected in the repairing strain. The loss of transforming activity and the frequency of mutations (up to 20-fold) was directly proportional to the amount of hydrocarbon bound to the DNA samples. The majority of the hydrocarbon-induced mutations were unable to revert spontaneously. In a second experiment, tritiated 7-BrMeBA-treated UV-irradiated DNA was exposed to highly purified rat liver endonuclease. This DNA sustained single-strand nicks in proportion to the amount of bound hydrocarbon, while untreated DNA remaining substantially intact. The action of the endonuclease appeared to result in

an increase in the biological activity of DNA containing hydrocarbon residues when this was assayed in the hcr⁻ mutant.

0081 ASSESSING THE HAZARD FROM BCME IN FORMALDEHYDE-CONTAINING ACRYLIC EMULSIONS. (E.) Hurwitz, M. D. (Rohm and Haas Co., Spring House, Pa.). *Am Dyestuff Reporter* 63(3):62-64, 77, 1974.

Thermosetting emulsion polymers used for the bonding of nonwoven fabrics are potential sources of bis(chloromethyl)ether, a carcinogen. Experiments were conducted to determine the potential evolution of this carcinogen from a typical nonwoven binder comprising ethyl acrylate and methylol acrylamide. Results indicated that bis(chloromethyl)ether was evolved from the drying and curing of the thermosetting emulsion polymer (no filter present). Ammonium chloride catalyst increased the evolution by a factor of 4, while ammonium nitrate had little effect. However, when the emulsion polymer was dried and cured on cellulosic web, both in the laboratory and in the mill, no bis(chloromethyl)ether was detected at the sensitivity level of 0.2 ppb. Since the potential for bis(chloromethyl)ether increases with available chloride and formaldehyde, it is prudent to minimize these reactions in any textile formulation. It is also recommended that working areas be monitored to insure that ventilation is adequate.

0082 GROUP ANALYSIS OF VOLATILE AND NON-VOLATILE N-NITROSO COMPOUNDS. (E.) Fine, D. H. (Thermo Electron Corp., Waltham, Mass.), F. Rufe and D. Lieb. *Nature* 247(5439):309-310, 1974.

A group-specific N-nitro compound analyser has been developed which can detect at the µg/kg level without requiring preconcentration or purification, thus making analysis of non-volatile N-nitroso compounds possible. The compound, dissolved in dichloromethane, is injected into a flash heater and swept by argon to a catalytic pyrolysis chamber where the N-nitroso compound is selectively cleaved. Pyrolysis products are prepared for use in an infrared-sensitive photomultiplier tube which is unable to detect emissions at wavelengths shorter than 0.6 µm. The output of the tube is amplified; the intensity of light emission is directly proportional to the number of mol of N-nitroso compound introduced to the instrument. Linear calibration curves were obtained for methylnitrosamine, ethyl-N-nitrososarcosinate, diethylnitrosamine, dibutylnitrosamine, diphenylnitrosamine, N-nitroso-N-ethylaniline, and phenylnitrosourea. No false positives were detected using a variety of compounds with structures similar to the N-nitroso compounds. Recovery experiments using dimethylnitrosamine and diphenylnitrosamine at the µg/kg level were in the range of 75 to 100%. Since the instrument has been demonstrated to be specific to N-nitroso compounds, selectivity to individual N-nitroso compounds

would be possible if N-nitroso compounds were separated from each other before introduction into the analyser.

0083 NEGATIVE OUTCOME OF A BLIND ASSESSMENT
OF THE ASSOCIATION BETWEEN SPRAY ADHESIVE
EXPOSURE AND HUMAN CHROMOSOME BREAKAGE. (E.) Hook,
E. B. (Birth Defects Inst., New York State Dept.
Hlth, Albany), N. H. Hatcher, P. S. Brinson,
O. J. Stanecky, L. Fisher, G. Feck and P. Greenwald.
Nature 249(5453):165-166, 1974.

Eleven individuals with histories of recent exposure to spray adhesives were matched with controls of the same age and sex. Blood specimens were cultured; about 36 metaphase plates were examined from each individual. No significant differences were found between the two groups. In fact, the observed frequency of breaks in the exposed subjects excluded with 95% confidence a rate 5 times or greater than that observed in the controls, which had been the order of magnitude of the increase reported previously. Repeating the study of 4 of the original 11, in whom the exposure had been the heaviest, again yielded no satisfactory differences between exposed and control subjects. The results in the exposed excluded with 95% confidence a rate twice or more than observed in the controls. On the basis of these results it is suggested that there is no reason currently to accept a purported association of significant magnitude between chromosome breakage and exposure to spray adhesives.

0084 STREPTONIGRIN INHIBITION OF 3-METHYL-
CHOLANTHRENE TRANSFORMATION *IN VITRO*.
(E.) Price, P. J. (Microbiol. Assoc., Bethesda,
Md.), W. A. Suk, G. J. Spahn, M. A. Chirigos, J. A.
Lane and R. J. Huebner. *Proc Soc Exp Biol Med*
145(4):1197-1200, 1974.

The ability of the antibiotic streptonigrin (Sn) to inhibit *in vitro* transformation of high-passage rat embryo cells by 3-methylcholanthrene (3-MC) has been studied in Fischer rats. The maximum nontoxic dose of Sn was 0.16 ng/ml. Incorporation of 0.33 or 0.66 ng of Sn into the growth medium reduced the relative plating efficiency by 39 and 51%, resp. However, resistant cells were selected at both levels and, when tested after 5 subcultures in the presence of Sn, the relative plating efficiency rose to 100% with 0.33 ng and 68% with 0.66 ng/ml. Duplicate cultures treated with 0.1 and 0.5 µg 3-methylcholanthrene, in the absence of Sn, showed transformed foci one and three vertical subcultures, resp. After 27 population doublings, all 3 levels of Sn protected the cells from transformation by 3-MC. Cultures transformed by 0.1 mg 3-MC produced tumors at the inoculation site in 13 of 13 untreated newborn rats within 56 postinoculation days. Cultures protected from transformation by Sn did not produce tumors. Thus, Sn was very effective in nanogram amounts in the protecting of cells from chemically induced transformation. The protective mechanism is not known, but it is

known that the chemical carcinogen itself can transform the cells. It is suggested that the high-passage cells can be transformed by the chemical carcinogen in the absence of added virus due to a reduction in the cellular control of the endogenous virus.

0085 ENVIRONMENTAL HEALTH. (E.) Anonymous.
Asbestos 55(6):8-20, 1973.

The Advisory Committee on Asbestos Cancers has concluded that levels of asbestos dust in the environment are not dangerous to the general public; that risk to the individual worker in the asbestos industry varies with the type of fiber, type of occupation, and extent of engineering controls implemented in the factory; that the amount of asbestos present in the water supply, beverages, food, or fluids used in administering drugs is not significant to cause an increased risk of disease; and that cigarette smoking greatly increased the risk of lung cancer among persons exposed to excessive asbestos dust during performance of their occupations. A recent Bureau of Mines investigation showed the asbestos fiber concentration in the air is low at the mines, but high in the mills. Asbestos industry standards for emission are being formulated in Canada. New equipment has been developed to enable safer asbestos handling with less human exposure to the fibers.

0086 ANOTHER LOOK AT COFFEE DRINKING AND CAN-
CER OF THE URINARY BLADDER. (E.) Bross,
I. D. J. (Roswell Park Mem. Inst., Buffalo, N.Y.)
and J. Tidings. *Preventive Med* 2(3):445-451, 1973.

A group of 360 white males and 120 white females with bladder cancer were investigated as to their coffee drinking habits, ethnic background, occupation, family history of cancer, smoking history and dietary habits. When age, sex, and smoking were controlled, the relative risk for males drinking one or more cups of coffee/day was 1.46 when compared to those drinking none or less than 1 cup/day. For women this risk was 0.80. After adjusting for cigarette smoking, this relationship remained. It was noted that, among the bladder cancer patients, there was an absence of persons who drank little or no coffee. Thus, the question exists as to whether there is a real relation between coffee drinking and bladder cancer or if there is an extraneous variable related both to coffee drinking and to bladder cancer. Two factors noted in this study are suggested in evidence that no direct relation to coffee drinking and bladder cancer exists. First, no dose-response relationship was established with the amount of coffee consumed. Secondly, those persons who reportedly did not drink coffee also did not smoke and thus the phenomenon is more probably associated with this sub-group of the population with unusual habits in these respects. These results, while not forming a concrete basis for a public health measure to restrict coffee consumption, do not, on the other hand, rule out the possibility of a causal relationship.

0087 INTERACTION OF N-METHYL-N'-NITRO-N-NITROSGUANIDINE WITH DNA AND HISTONE IN RAT TISSUES *IN VIVO*. (E.) Saito, T. (Med. Sch., Kyushu U., Fukuoka, Japan) and T. Sugimura. *Gann* 64(6):537-543, 1973.

The distribution of N-methyl-N'-nitro-N-nitrosoguanidines (MNNG) in various organs of rats and the *in vivo* incorporation of the radioactivities of MNNG into DNA and histone in rat tissues were studied using MNNG(guanidino- ^{14}C) and MNNG(methyl- ^{14}C). Radioactivity from MNNG(guanidino- ^{14}C) was mostly found in the stomach and intestine while that from MNNG(methyl- ^{14}C) was detected not only in the stomach and intestine but also in the liver and kidney. In the glandular stomach, radioactivity from MNNG(guanidino- ^{14}C) was incorporated into histone and that from MNNG(methyl- ^{14}C) into both DNA and histone, especially in the former. In the liver, however, radioactivity from MNNG(guanidino- ^{14}C) was not detected in histone but DNA was labeled with radioactivity from MNNG(methyl- ^{14}C). These results indicate that the extent of incorporation of MNNG(guanidino- ^{14}C) into the acid-insoluble materials in the tissues at the time when administration of MNNG was terminated is correlated with tumor formation and that the extent of MNNG(methyl- ^{14}C) incorporation is not. It is suggested that the greater values of acid-insoluble radioactivity from MNNG(guanidino- ^{14}C) in the glandular stomach immediately after its oral administration may be due to direct binding of MNNG with the tissues of the glandular stomach. With MNNG(methyl- ^{14}C) an intermediate may be produced and transferred to the liver.

0088 SMOKING AND CANCER. (E.) Burch, P. (The General Infirmary, Leeds, England). *New Sci* 62(892):41, 1974.

In 20 countries the association between death rates for lung cancer and per capita cigarette consumption are not significant for women and only weakly positive for men. In reviewing the evidence as received from necropsy series, the vast majority of the recorded increase in lung cancer of late has been due to changes in the level of diagnosis. It is suggested that genetic factors may determine the population susceptible to this disease. The hypothesis that stress might act in the manner of a precipitating carcinogen must be considered but is difficult to verify.

0089 FECAL BACTERIAL β -GLUCURONIDASE: CONTROL BY DIET. (E.) Reddy, B. S. (Naylor Dana Inst. Disease Prevention, New York, N.Y.), J. H. Weisburger and E. L. Wynder. *Science* 183(4123):416-417, 1974.

The effect of high meat and non-meat diets on the intestinal bacterial β -glucuronidase activity was studied in human volunteers. The mixed Western high meat diet was fed to 5 males and 1 female (aged 30-52 yr) and consisted of beef, pork, or chicken (454 g/day); vegetables; potato or rice; bread, cereal; fruit; milk; and butter. The

non-meat diet, fed to the same individuals contained eggs; skim milk; citrus fruit; other fruits; dried beans, peas, or nuts; vegetables; bread and cereals; potatoes, rice, or pasta; peanut butter, margarine and vegetable oil. The β -glucuronidase activity in the feces was significantly higher while subjects were eating the high meat diet, therefore, the intestinal microflora of individuals on high meat diets has a greater capability to hydrolyze glucuronic acid conjugates than that of individuals on a meat-free diet. Since glucuronide formation is a major detoxification mechanism in mammals, changes in the intestinal flora might alter the biological activity, toxicity, excretion, and resorption of many endogenous and exogenous compounds, including carcinogen metabolites, in the intestine.

0090 GAS VAPOUR PHASE CONSTITUENTS AND SH REACTIVITY OF CIGARETTE SMOKE INFLUENCE LUNG CULTURES. (E.) Leuchtenberger, C. (Swiss Inst. Exp. Cancer Res., Lausanne), R. Leuchtenberger and I. Zbinden. *Nature* 247(5442):565-567, 1974.

The effects of 2 types of cigarette smoke, containing the same amounts of particulate matter but differing in their content of gas vapor phase constituents, were studied on nearly 3,000 hamster lung cultures. Activated carbon was used to achieve a striking reduction of the gas vapor phase constituents and of the amount of SH groups present in one type of smoke. The content of nicotine and total particulate matter closely resembled that of the smoke from non-filtered cigarettes. Cultures exposed to nonfiltered smoke showed marked cytotoxic effects such as pycnosis, necrosis, cell death and a striking reduction of alveolar macrophages, followed by atypical growth and a high frequency of mitotic abnormalities. Cultures exposed to filtered smoke showed milder changes of all these features. Exposure to nonfiltered smoke greatly increased the DNA content in metaphase and telophase. There was no significant change in DNA content of cultures exposed to filtered smoke. Thus, exposure to hamster lung cultures to cigarette smoke with reduced gas vapor phase constituents and low SH reactivity produced less damage to the cells, less abnormal growth and less disturbance of DNA complement in the chromosomes than smoke with greater amounts of gas vapor phase constituents and higher SH reactivity.

0091 INTERACTION OF NITRITE WITH PROTEINS AT GASTRIC pH. (E.) Knowles, M. E. (Food Res. Inst., Norwich, England), D. J. McWeeny, L. Couchman and M. Thorogood. *Nature* 247(5439):288-289, 1974.

The possibility that interactions of nitrite with certain food components could cause formation of C-nitroso compounds whose biological behavior is largely unknown but which are much weaker carcinogens than the corresponding N-nitroso derivatives has been examined. The interaction of nitrite with

bovine serum albumin was studied under simulated gastric conditions. Both 3-nitrosotyrosine and 3,4-dihydroxyphenylalanine have been identified as products of this reaction. It is postulated that they are degradation products of 3-nitrosotyrosine and that the ϵ -amino groups of lysine are currently deaminated to yield 6-hydroxynoreleucine. These reactions show that, apart from nitrosamine formation, other nitrosation reactions involving nitrite in foodstuffs could take place under stomach conditions and yield modified amino acids.

0092 CARCINOGENIC RESPONSE OF BROOD SOWS FED AFLATOXIN FOR 28 TO 30 MONTHS. (E.)

Shalkop, W. T. (Div. Vet. Res., FDA, Beltsville, Md.) and B. H. Armbricht. *Am J Vet Res* 35(5):623-627, 1974.

Four brood sows were fed aflatoxicogenic cultures and an aflatoxin concentrate in the basal ration for 28 to 30 months. The dose rates of aflatoxins B₁ and G₁ were 35 μ g/kg body weight/day during growth period (8 months), 10 μ g/kg/day during gestation, and 40 μ g/kg/day during lactation (6 weeks). One sow, used as a control, received basal ration only. The only clinical sign in the 4 treated sows was a reduction in weight gain. Macroscopic changes involved only the liver in 3 of the 4 sows. Microscopic changes included hyperplastic nodules, as large as 6 mm diameter, in the livers of all treated sows. These nodules were composed of relatively normal hepatic cells, but without central veins or bile ducts. Nodular hepatocellular adenomas were commonly seen. In 1 sow there were metastases to the omentum by seeding of hepatocellular nodules and also intravascular metastases of undifferentiated neoplastic cells to the hepatic lymph nodes. Varying degrees of cirrhosis were noted in 3 of the sows, and was characterized in one by bile duct proliferation, fibrosis, and nodular hyperplasia, with many of the nodules undergoing central anoxic necrosis. Intravascular hepatic cell emboli were noted in livers of 3 sows. The emboli were degenerating in most instances. It is concluded that the hog requires a longer period of exposure to the carcinogenic effect of aflatoxin to produce hepatic cell carcinomas with systemic involvement by metastasis.

0093 URETHANE INTERACTION WITH NUCLEIC ACIDS AND PROTEINS FROM NON-MALIGNANT FAST

GROWING TISSUES. (E.) Bhide, S. V. (Tata Mem. Ctr., Cancer Res. Inst., Bombay, India). *Chem Biol Interact* 8(1):19-23, 1974.

The interaction of urethane metabolite(s) was studied with macromolecules from embryos of pregnant mice and from regenerating liver of mice following partial hepatectomy. Pregnant Swiss strain mice were treated with tritiated urethane on day 17 of the pregnancy. Mice subjected to partial hepatectomy were injected with tritiated urethane 6 hr before killing and were studied 72 and 198 hr after the operation had been performed. It was noted that the specific radioactivity of lung DNA was highest in pregnant mice. Fast growing embryos from pregnant mice did not show

a higher specific radioactivity for DNA compared with lung DNA. Therefore, in pregnant mice, urethane interaction with DNA retains tissue specificity even in the presence of a fast growing embryo. In partially hepatectomized mice, the specific radioactivities of lung DNA and regenerating liver DNA were comparable. It was noted that binding to macromolecules was greatest at 72 hr when the highest mitotic activity in regenerating liver occurs. It seems probable that the reaction of urethane metabolites with DNA is influenced by the mitotic activity of the regenerating liver.

0094 EFFECT OF THIOCYANATE ON NITROSATION OF AMINES. (E.) Boyland, E. (London Sch.

Hygiene Tropical Med., England) and S. A. Walker. *Nature* 248(5449):601-602, 1974.

The formation of nitrosamines in the human stomach is a carcinogenic hazard to man. Thiocyanate, secreted in the saliva, catalyzes the nitrosation reaction under acid conditions, such as gastric juice, between pH 1 and 2. In non-smokers the saliva contains about 50 mg/l, but this increases 3 to 4 times in smokers. The thiocyanate concentration in stomachs of non-smokers measures about 0.2 mM and 0.6 mM in smokers, which would increase nitrosation 100 and 300 times, resp. Saliva also contains up to 200 mg/l of nitrate, derived from food, water and tobacco smoke. Cigarette smoke contains cyanide compounds readily converted to thiocyanate in the body by action of rhodanese (thiosulphate-sulphur transferase). Smoke containing up to 0.5 mg cyanides yields double this amount of thiocyanide. Smoking apparently changes the route of thiocyanate excretion, either by inhibition of kidney secretion or by stimulation of salivary secretion. Although cigarette smoke inhibits rhodanese activity of guinea pig tissues, it increases the thiocyanate concentration of the salivary glands, lung, kidney, and brain. This is because rhodanese activities are high and smoke contains cyanide compounds. Nitrosamines are formed in cigarette smoke by the reaction of oxides of nitrogen with secondary and tertiary amines. The synthesis of nitrosamines in the stomach is probably greater in smokers due to the hydrocyanic acid and oxides of nitrogen present in tobacco smoke.

0095 INHIBITION OF AFLATOXIN PRODUCTION AND TENTATIVE IDENTIFICATION OF AN AFLATOXIN

INTERMEDIATE "VERSICONAL ACETATE" FROM TREATMENT WITH DICHLORVOS. (E.) Schroeder, H. W. (Agr. Res. Serv., U.S. Dept. Agr., College Station, Tex.), R. J. Cole, R. D. Grigsby and H. Hein, Jr. *Appl Microbiol* 27(2):394-399, 1974.

Low-aflatoxin-producing (*Aspergillus flavus*) and high-aflatoxin-producing (*A. parasiticus*) strains of fungus were grown in the presence of the insecticide dichlorvos (0, 5, 10, 15, or 20 μ g/ml, w/v basis). Dichlorvos at all four concentrations inhibited aflatoxin B₁ production by three isolates of *A. flavus* and one isolate of *A. parasiticus*. With the *A. parasiticus* isolate and two of the *A.*

flavus isolates, dichlorvos at 5 µg/ml reduced aflatoxin production approximately 90%; increasing insecticide concentrations decreased aflatoxin yields further but at a sharply reduced rate. Aflatoxin B₂ yields were decreased proportionately, as were yields of aflatoxin G₁ and G₂ by *A. parasiticus*. In a fourth *A. flavus* isolate, dichlorvos at the 5 µg/ml level stimulated aflatoxin production, which was inhibited by higher dose levels. The higher insecticide concentrations delayed sporulation in the various isolates. Reductions in the production of aflatoxins were accompanied by the appearance of an orange pigment, the concentration of the pigment increasing in direct proportion to the reduction in aflatoxin production. Spectral analyses of the pigment and its methylated and acetylated derivatives showed it to be versiconal acetate (IV). The data suggest that IV is an intermediate in the metabolic cycle that may terminate in the production of aflatoxin or the versicolorins, or both. Dichlorvos apparently inhibits the biosynthesis of the difurano ring structure common to the aflatoxins and versicolorins.

0096 USE OF DNA REPAIR SYNTHESIS IN DETECTING ORGANOTROPIC ACTIONS OF CHEMICAL CARCINOGENS. (E.) Stich, H. F. (Cancer Res. Ctr., U. British Columbia, Vancouver, Canada) and D. Kieser. *Proc Soc Exp Biol Med* 145(4):1339-1342, 1974.

A novel approach to the study of the organotropic action of chemical carcinogens and mutagens was undertaken in 6 week old C3/H mice. The compounds under study, 4-nitroquinoline-1-oxide and dimethylnitrosamine, were applied *in vivo* and their effects on the DNA of various cell types were estimated by measuring the level of DNA repair synthesis *in vitro*. A DNA repair synthesis, which follows the carcinogen-induced DNA alterations, occurred only in those tissues from which neoplasms arose. No detectable DNA repair synthesis was observed after application of the nononcogenic 4-nitroquinoline-1-oxide metabolite, 4-aminoquinoline-1-oxide. This *in vivo* and *in vitro* combination system may be a suitable tool to detect organotropic carcinogens and to identify tissues which may give rise to neoplasms.

0097 CYTOLOGIC CHANGES OF THE RESPIRATORY EPITHELIUM IN IRON FOUNDRY WORKERS. (E.) Plamenac, P. (Med. Fac., U. Sarajevo, Yugoslavia), A. Nikulin and B. Pikula. *Acta Cytol* 18(1):34-40, 1974.

A cytologic exam of sputum specimens in 47 workers (aged 24-47 yr) in one iron foundry was made. All persons were non-smokers, with normal chest roentgenograms and without indications of any acute or chronic respiratory or other organic disease. According to the type of harmful inhalations considered, the individuals fell into 3 classes. In the first were 15 workers who were generally exposed to the influence of high temperatures. Secondly there were 10 workers exposed to between 3,240 and 22,000 particles in 1 ccm of air with no hot air exposure. The third

category included 22 workers exposed to hot air and a number of particles in 1 ccm of air ranging between 1,800 and 2,560. The dusts varied between 40-65% iron, mostly as Fe₂O₃. In a significant number of cases respiratory spirals and eosinophilic leukocytes were present in the sputa. In almost all cases hemosiderin containing macrophages were present. Abnormal columnar cell findings were present in all individuals. Squamous metaplasia was noted in 2/3 of the cases, of which about half were associated with cellular atypia. Thus, long term exposure to these three types of irritants can produce extensive alterations of bronchial epithelium.

0098 EXPOSURE RULES EASED. (E.) Anonymous. *Chem Week* 114(6):14, 1974.

The Occupational Safety and Health Administration issued permanent standards governing exposure to 14 suspected carcinogens. For the allegedly more potent carcinogens (4-aminodiphenyl, benzidine and its salts, 4-nitrobiphenyl, beta-naphthylamine, bischloromethyl ether, and methyl chloromethylether), there are no restrictions covering solid and liquid mixtures containing less than 0.1% by weight or volume. Alpha-naphthylamine and beta-naphthylamine standards do not restrict operations involving destructive distillation of carbonaceous materials. The tolerance for 8 supposedly less carcinogenic chemicals, 2-acetylaminofluorene, 3,3'-dichlorobenzidine, 4-dimethylaminoazobenzene, alpha-naphthylamine, N-nitrosodimethylamine, beta-propiolactone, ethylene imine and MOCA, is 1%.

0099 UPTAKE OF METHYLCHOLANTHRENE IN THE RAT PANCREAS. (E.) Black, O., Jr. (VA Hosp., August, Ga.) and P. D. Webster, Ill. *Am J Dig Dis* 19(1):37-42, 1974.

The chemical carcinogen, 3-methylcholanthrene, was injected (5 µCi, i.p.) into white male Sprague-Dawley rats to determine to what extent rat pancreas sequesters and metabolizes this drug. The carcinogen was taken up in the pancreas to the same degree as the liver on a per gram wet weight basis. The majority of the binding was to the membranous components with only 17% remaining in the supernatant fraction. Maximal incorporation occurred around 36 hr following administration. Ether extracts of homogenates showed that few breakdown products were formed even up to 48 hr after injection. It thus appears that rat pancreas sequesters 3-methylcholanthrene, but has little metabolizing capacity.

0100 MUTAGENICITY OF ETHYLENE CHLOROHYDRIN. A DEGRADATION PRODUCT PRESENT IN FOODSTUFFS EXPOSED TO ETHYLENE OXIDE. (E.) Rosenkranz, H. S. (Coll. Phys. Surg., Columbia U., New York, N.Y.) and T. J. Wlodkowski. *J Agr Food Chem* 22(3):407-409, 1974.

Ethylene chlorohydrin (2-chloroethanol) was muta-

genic for *Salmonella typhimurium* TA 1530 and TA 1535, but not for TA 1538. This activity was dependent on the concentration. Ethylene chlorohydrin also preferentially blocked the growth of DNA polymerase deficient *E. coli*. The activity of this chemical was of the same order of magnitude as that of the mutagens 4-nitroquinoline N-oxide and methylmethanesulfonate. The mechanism by which ethylene chlorohydrin alters the DNA of living cells is unknown. Results currently indicate that exposure of DNA to 2-chloroethanol result in drastic alterations of the physical chemical properties of the biopolymer. The presence of elevated levels of ethylene chlorohydrin, 1000 ppm, in foodstuffs sterilized with ethylene oxide, calls for investigation of effects of this substance and the potential hazard of human exposure.

0101 SOME FACTORS AFFECTING THE HOST-MEDIATED ASSAY RESPONSE. (E.) Zeiger, E. (Food Drug Admin., Washington, D.C.). *Environ Health Perspect* (6):101-109, 1973.

Mice were injected i.p. with *Salmonella typhimurium* his G-46 (a missense mutant), and, in some cases, aminoacetonitrile (AAN). One hour later, they were injected i.m. with dimethylnitrosamine (DMNA), N-nitrosomorpholine (NM), or N-nitroso-N-methylurea (NMU). Mice maintained on a complete semisynthetic diet (SSD) for 6-8 days yielded a depressed mutagenic response to DMNA and NM when compared to chow-fed mice; the effects with NMU were contrary to those with DMNA and NM but were nonsignificant. Maintenance of the mice on a protein-free diet for 8 days resulted in a dramatic depression in the mutagenic response to DMNA when compared to mice maintained on SSD. NM yielded an initial enhancement of mutagenicity followed by depression. Starvation for 24 hours following SSD feeding produced an enhanced mutagenic response to DMNA and NM. Both DMNA and NM mutagenicity were enhanced by feeding pure casein for 24 hours following SSD feeding; the mutagenic response to NMU was strongly depressed under these conditions. AAN depressed the mutagenic response to DMNA and NM, the responses obtained with DMNA appearing dose related. The level of AAN causing the greatest inhibition of the mutagenic response to DMNA and NM yielded the greatest enhancement of NMU mutagenicity. Treatment with AAN and DMNA appeared to result in selection for the *his+* revertant; otherwise, there was no indication of a selective advantage for either the *his+* revertant or the parental *S. typhimurium* G-46. The results indicate that the carcinogenic, mutagenic, and hepatotoxic effects of DMNA may be responses to the same chemical substance.

0102 ETHIONINE CARCINOGENESIS: ITS MODIFICATION BY DIETARY CHANGES IN MAJOR NON-PROTEIN CARBON SOURCES. (E.) Vann, L. S. (Arequipa Fdn., Palo Alto, Cal.). *Proc West Pharmacol Soc* 17:251-255, 1974.

Male Wistar rats were studied in whose diets most

or all of the 75% dietary sucrose was replaced by other non-protein nutrients, and the subsequent effect on ethionine carcinogenesis was observed. Ethionine (0.3%) was incorporated into each of 4 different diets: sucrose; glycerol, propylene glycol, sucrose; glucose; and fructose. Gross examination of the liver indicated that the non-protein carbon source influenced the number and size of nodules that occurred, and that it is in these nodules that the neoplastic changes develop. In general, relative to the length of feeding periods, the amount of ethionine consumed and the type, number, and degree of neoplastic changes, ethionine was most carcinogenic when part of the fructose diet and least carcinogenic when part of the glycerol, propylene glycol diet. A rough correlation appeared between increasing liver size and the degree of neoplastic change occurring. The period of adjustment to the diet saw animals on the glycerol, propylene glycol diet undergo the most extensive metabolic changes but noted that the metabolism which did evolve was either less compatible with or somehow modified the changes associated with ethionine induced nodule formation and related neoplastic changes, despite the highest ethionine intake. Fructose ingestion required the most extensive metabolic modifications, but these modifications, after the shortest dietary period, were very conducive to nodule formation and bile duct carcinoma.

0103 MUTAGENIC AND RECOMBINOGENIC ACTIVITIES OF THE FOOD ADDITIVE FURYLURAMIDE IN EUKARYOTES. (E.) Ong, T.-M. (Nat'l. Inst. Environmental Health Sci., Research Triangle Pk., N.C.) and M. M. Shahin. *Science* 184(4141):1086-1087, 1974.

The mutagenic and recombinogenic activities of furyluramide (AF-2), an antimicrobial food additive, were tested in a two-component heterokaryon of *Neurospora crassa* and a diploid strain of *Saccharomyces cerevisiae*, respectively. The mutation frequency in *N. crassa* increased with increasing AF-2 concentration, and at AF-2 concentrations greater than 5 µg/ml, the survival of the conidia decreased linearly with increasing concentration. In *S. cerevisiae*, the number of aberrant colonies increased as a function of incubation time with AF-2. Thus, AF-2 causes genetic alterations in eukaryotes and is a potent mutagen. The possible mutagenic, carcinogenic, and teratogenic effects of AF-2 in man should be studied and its use as a food additive reevaluated.

0104 NICOTINE INHIBITION OF THE METABOLISM OF 3,4-BENZOPYRENE, A CARCINOGEN IN TOBACCO SMOKE. (E.) Weber, R. P. (Jefferson Med. Coll., Philadelphia, Pa.), J. M. Coon and A. J. Triolo. *Science* 184(4141):1081-1083, 1974.

Male Sprague-Dawley rats were treated with a single i.p. injection of nicotine bitartrate (25 mg/kg), after which ¹⁴C-labeled 3,4-benzopyrene (BP) was injected i.v. and the biliary excretion of BP metabolites monitored. The nicotine treatment resulted in a significant decrease in

the biliary excretion of radioactive metabolites of BP. In a second experiment, the benzopyrene hydroxylase activity was measured in homogenates of liver, lung, and small intestine prepared from rats which had been treated 24 hours earlier with nicotine. The nicotine pretreatment decreased the enzyme activity in these tissues. The addition of nicotine to incubated tissues also decreased the activity of benzopyrene hydroxylase in them. Thus, nicotine inhibits the *in vivo* and *in vitro* metabolism of 3,4-benzopyrene.

- 0105 ENZYMATIC AZIRIDINE SYNTHESIS FROM β -AMINOALCOHOLS - A NEW EXAMPLE OF ENDOGENOUS CARCINOGEN FORMATION. (E.) Bicker, U. (Erfurt Med. Acad., Germany) and W. Fischer. *Nature* 249(5455):344-345, 1974.

The enzymatic formation of 1,2-dimethyl-2-phenylaziridine (III) from the corresponding β -aminoalcohol (IV), an isomer of ephedrine, was studied. IV was added to the supernatant of a liver homogenate prepared from a female Hauben rat and allowed to react for 2.5 hours at 37 C. Ethanol was then added to the mixture and the resulting precipitate removed. The supernatant was adjusted to pH 8 and incubated at 37 C for 1 hour. The alkaline solution was then extracted with ether and the basic compounds separated by extraction with 2N H₂SO₄. The concentrate thus obtained was analyzed by means of thin-layer chromatography on silica gel. III was detected at this time, but could not be detected when the solution was allowed to stand overnight in 2N H₂SO₄; this indicated ring-opening to IV. Since III was not formed with SO₄²⁻ and ATP was not added to the reaction mixture, it was concluded that the aziridine is formed enzymatically from the β -aminoalcohol.

- 0106 INDUCTION OF TUMORS OF THE STOMACH AND ESOPHAGUS IN INBRED CHINESE HAMSTERS BY ORAL DIETHYLNITROSAMINE. (E.) Baker, J. R. (Mason Res. Inst., Worcester, Mass.), M. M. Mason, G. Yerganian, E. K. Weisberger and J. H. Weisburger. *Proc Soc Exp Biol Med* 146(1):291-293, 1974.

Male and female strain M Chinese hamsters were given 40 ppm/day of diethylnitrosamine (DEN) in their drinking water for periods of 17 to 26 weeks. The males and females responded similarly in all respects to the carcinogen, the survival time in both sexes averaging 145 days. Liver nodules diagnosed as extensive cirrhosis were seen in 60% of the hamsters, hepatocellular carcinomas were seen in 5 animals, one animal developed a hemangiosarcoma of the spleen, and tumors of the forestomach and esophagus were present in all of the animals. Most of the stomach and esophageal tumors were papillomas, although 23% of the gastric tumors and 15% of the esophageal tumors were squamous carcinomas. Biopsies from abnormal liver fragments gave rise to two rapidly proliferating cell lines: a diploid fibroblastlike cell line; and an epithelioid cell line with a pseudodiploid karyotype, 2n=22. The highly inbred Chinese hamster appears to be a suitable model for

studies involving carcinogenesis in the esophagus and stomach.

- 0107 TRANSPLACENTAL ACTION OF SOME NITROSO-COMPOUNDS ON ORGANO-TYPICAL CULTURES OF WISTAR RAT EMBRYONIC KIDNEY TISSUE. (E.) Shabad, L. M. (Acad. Med. Sci. USSR) and N. I. Golub. *Bull Exp Biol Med* 76(9):1087-1090, 1974.

The transplacental action of dimethylnitrosamine (DMNA) and N-nitrosomethylurea (NMU) on organo-typical cultures of Wistar rat embryonic kidney tissue was studied. The cultures were prepared from tissue explants taken from rats injected with DMNA or NMU in the last week of pregnancy. The DMNA and NMU treated cultures showed a higher rate of survival than the nontreated cultures. While the control cultures morphologically resembled organ cultures of mouse kidney, morphological changes were fairly common among the DMNA and NMU treated cultures. These changes included structural outgrowths and hyperplastic epithelial lesions, the latter never occurring in the control cultures. The hyperplastic epithelial lesions included diffuse and focal proliferation, layers of atypical epithelium, and, in cultures treated with DMNA, cystic and papillary formations resembling cystadenomas. Hyperplastic changes were more marked in the DMNA treated cultures than in the NMU treated cultures.

- 0108 STUDIES ON CARCINOGENIC AZO DYES. III. RETENTION OF TRITIUM DURING ENZYMATIC HYDROXYLATION OF 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE(4'-³H, OR 5'-³H) OR CHEMICAL SUBSTITUTIONS OF THE RELATED COMPOUND, AND THE EFFECT OF THE REPEATED ADMINISTRATION OF THIS AZO DYE ON THE RETENTION OF TRITIUM. (E.) Mori, Y. (Gifu Coll. Pharmacy, Japan), K. Toyoshi and S. Baba. *Chem Pharm Bull (Tokyo)* 21(12):2577-2584, 1973.

The retention of tritium during the enzymatic hydroxylation at the 4' position of 3'-methyl-4-dimethylaminoazobenzene(4'-³H, or 5'-³H) (3'-Me-DAB) and during nonenzymatic substitutions at the 4 position of 3-methylacetanilide(4'-³H, or 5'-³H) is reported, as is the effect of the repeated administration of 3'-Me-DAB to rats on the aryl hydroxylation activity against 3'-Me-DAB(5'-³H) and retention of tritium in the hydroxylated product. The enzymically formed 3'-methyl-4'-hydroxy-4-dimethylaminoazobenzene from 3'-Me-DAB(4'-³H) retained an average of 94% tritium. The NIH shift also occurs in the enzymatic hydroxylation of 3'-Me-DAB(4'-³H). The chemically produced 4-hydroxy-, 4,6-dibromo-, and 4-nitro-3-methylacetanilide from 3-methylacetanilide(4'-³H) retained tritium approximately 65% in each case. Since no significant effect of feeding 0.06% 3'-Me-DAB for 1-4 weeks on the aryl hydroxylation activity against 3'-Me-DAB(5'-³H) and retention of tritium in the hydroxylated product from 3'-Me-DAB(4'-³H) was observed, it is suggested that the aryl hydroxylase activity of rat liver against 3'-Me-DAB dose not be qualitatively changed during the early stage of the carcinogenesis by 3'-Me-DAB.

- 0109 FORMATION OF BIS(CHLOROMETHYL) ETHER FROM FORMALDEHYDE AND HYDROGEN CHLORIDE. (E.) Frankel, L. S. (Rohm and Haas Co., Philadelphia, Pa.), K. S. McCallum and L. Collier. *Environ Sci Technol* 8(4):356-359, 1974.

The formation of bis(chloromethyl)ether (BCME) from formaldehyde and hydrogen chloride in moist air was investigated by combining measured amounts of monomeric formaldehyde and hydrogen chloride with air in glass vessels or Saran bags. The resulting amount of BCME was determined by high resolution mass spectrometry and verified by gas chromatography/mass spectrometry or dual column gas chromatography. Gaseous formaldehyde and hydrogen chloride reacted in the ambient moist air to form BCME in yields of about .01 mol%. The amount of BCME formed was relatively insensitive to moderate changes in temperature and humidity, but was strongly dependent on the reactant concentrations. Steady state conditions did not seem to be attained in less than 18 hours. BCME was also found in the vapors forming over formalin slurries containing Friedel-Crafts chloride salts. After 18 hours, the BCME concentrations ranged from 210 ppb for formalin slurries prepared with FeCl_3 to 1500 ppb for slurries prepared with AlCl_3 . These results are of interest in light of the recently reported carcinogenicity of BCME.

- 0110 INDUCTION OF NEUROGENIC TUMORS IN C3HeB/FeJ MICE BY NITROSOUREA DERIVATIVES: OBSERVATIONS BY LIGHT MICROSCOPY, TISSUE CULTURE, AND ELECTRON MICROSCOPY. (E.) Denlinger, R. H. (Dept. Vet. Pathobiol., Ohio State U., Columbus), A. Koestner and W. Wechsler. *Int J Cancer* 13(4):559-571, 1974.

Neurogenic tumors were induced in 32.3% of C3HeB/FeJ mice treated transplacentally with ethylnitrosourea and in 10.5% of mice treated i.v. with methylnitrosourea. Reports of earlier experiments have indicated that non-neural tumors, particularly lymphomas, were readily induced on other strains of mice treated with nitrosourea derivatives. However, tumors of the nervous system occurred in only a low percentage of treated mice in this study. Genetic strain of mice appears to have some effect on the susceptibility of mice to nitrosoureas. In 19 adult male mice treated i.v. every 4 weeks with 25 mg/kg of methylnitrosourea to a total dose of 175 mg/kg, 2 brain tumors, an oligodendroglioma in the diencephalon and a mixed neuroblastoma-glioma of the cerebellum, occurred. Neurinomas of cranial nerves developed in 9 of 31 offspring of pregnant mice treated with 20 mg/kg ethylnitrosourea i.v. on the 19th day of gestation. One methylnitrosourea-induced oligodendroglioma and 1 ethylnitrosourea-induced neurinoma were propagated in tissue culture. Cells of both tumors produced intracerebral and subcutaneous tumors following injection into syngeneic mice. Tissue samples from both intracerebral transplanted tumors contained abundant clusters of C-type RNA viruses in interstitial spaces. Budding virus particles were readily demonstrated on the plasma membranes of tumor cells.

- 0111 NINETY DAY SUBCHRONIC TOXICITY OF N-2-FLUORENYLACETAMIDE (2-FAA) IN C57BL/6j and BALB/cStCr1BR MICE. (E.) Haley, T. J. (Nat'l. Ctr. Toxicol. Res., Jefferson, Ark.), G. Schieferstein, J. R. Harmon, K. L. Dooley, W. E. Jaques, C. Frith and J. H. Farmer. *Proc Soc Exp Biol Med* 146(2):648-651, 1974.

Subchronic (90-day) toxicity of N-2-fluorenylaceta-mide was investigated in male and female C57BL/6j and BALB/cStCr1BR strain mice. No signs of toxicity were noted with dietary levels ranging from 0.001-0.05% N-2-fluorenylaceta-mide. A dose dependent urinary bladder epithelial hyperplasia was noted in both strains with the males more susceptible than the females. Squamous metaplasia of the urinary bladder was observed in the BALB/c mice with the male response double that of the female response. One urinary bladder carcinoma was found in a BALB/c male at the 0.025 and 0.05% N-2-fluorenylaceta-mide levels. Adrenal gland spindle cell hyperplasia was observed in both males and females of both strains, more pronounced in females, and was not dose related. Urinary bladder concretions were noted in the males of both strains in all groups including controls, and were not dose related. No other significant histopathological changes were observed.

- 0112 A SIMPLE METHOD FOR THE DETECTION OF MUTAGENS IN URINE: STUDIES WITH THE CARCINOGEN 2-ACETYLAMINOFLOURENE. (E.) Durston, W. E. (Biochem. Dept., Univ. California, Berkeley) and B. N. Ames. *Proc Natl Acad Sci USA* 71(3):737-741, 1974.

A simple test on petri plates was used to detect mutagenic metabolites in urine. The addition of commercial beta-glucuronidase to the petri plates along with the urine, liver homogenate, and bacteria allows detection of metabolites that are excreted in urine as beta-glucuronide conjugates. This method was used to demonstrate the mutagenic activity with urine of male albino Sprague-Dawley rats that were administered as little as 200 μg (1.6 mg/kg) of the carcinogen, 2-acetylaminofluorene. The major metabolite detected in these experiments was apparently a glucuronide conjugate. It was suggested that this method be used for screening human urine in order to detect mutagenic metabolites of drugs and of dietary components. It may also be useful for testing of urinary metabolites of drugs and food additives in experimental animals.

- 0113 MUTAGENICITY EXPERIMENTS WITH THE TRANQUILLIZER MEPROBAMATE IN *DROSOPHILA MELANOGASTER* AND IN HUMAN LEUKOCYTE CHROMOSOMES *IN VITRO*. (E.) Luers, H. (Genetics Inst., Free Univ. Berlin, Germany), E. Vogel and G. Obe. *Experientia* 30(3):310-312, 1974.

The effect of meprobamate on *Drosophila melanogaster in vivo* and human leukocyte chromosomes *in vitro* was studied to determine whether the drug might exhibit mutagenic activities by inhibiting DNA synthesis and repair processes. In *Drosophila*

results with the Base-technique did not show any elevation of the recessive lethal frequency over the baseline after application of meprobamate p.o. or by injection. The rates of semilethals and of visible mutations did not show any difference to the control level. Except for one male in one experiment, no clusters of mutations were found. The distribution of the lethals approximates a spontaneous distribution in that there are 2 peaks, one at the left end, the other at the right of the X-chromosome. In tests evaluating chromosome aberrations, no increase in the aberration frequencies was noted. Thus meprobamate also remained ineffective with respect to the induction of chromosome aberrations in mature sperm. In experiments on human chromosomes, no chromosome breaking ability of meprobamate was noted on human leukocytes *in vitro*. The doses used in these tests were significantly greater than the doses used therapeutically.

0114 ALTERATION OF PROTEIN DEGRADATION IN MITOCHONDRIA AND OTHER RAT LIVER FRACTIONS AS A RESULT OF AMINOAZO DYE FEEDING. (E.) Fiala, E. S. (Shepherd Coll., Shepherdstown, W. Va.), W. G. Kettering and S. Fiala. *Biochim Biophys Acta* 338(1):43-56, 1974.

Relative rates of protein degradation were examined in liver fractions of male Sprague-Dawley rats after prolonged feeding of 3'-methyl-4-dimethylaminoazobenzene and its non-carcinogenic isomer, 2-methyl-4-dimethylaminoazobenzene. After continual feeding for 50-63 days, both azo dyes decreased the rates of protein degradation of all liver fractions studied. 2-Methyl-4-dimethylaminoazobenzene showed the more pronounced effect. The accumulation of rat liver mitochondria from prolonged feeding was attributed to decreased degradation rather than increased biogenesis. In the presence of sodium dodecylsulfate, mitochondrial protein subunits could be separated by Sepharose gel chromatography into 2 distinct fractions: a fairly homogeneous high molecular weight fraction characterized by a low turnover and low degree of 2-methyl-4-dimethylaminoazobenzene binding, and a heterogeneous lower molecular weight fraction with high turnover and higher degree of 2-methyl-4-dimethylaminoazobenzene binding. The pronounced effect of the noncarcinogenic 2-methyl-4-dimethylaminoazobenzene on rat liver may provide a convenient and useful system in which the mechanism of protein degradation in the mammalian cell can be studied.

0115 EFFECT EXERTED BY VARIOUS ANDROGENS ON LIVER CANCER INDUCED IN THE RAT BY p-DIMETHYLAMINOAZOBENZENE (DAB). (Fr.) Corre-Hurst, L. (Radium Inst., Paris, France), J. M. Plouchard and M.-F. Jayle. *C R Acad Sci (Paris)* 277(21):2441-2443, 1973.

Five groups of adult male Wistar rats were fed diets containing 0.6 g/kg of p-dimethylaminoazobenzene (DAB) plus 0.020 g/kg of either testosterone, androsterone, androsterone plus sodium sulfate, retro-

testosterone, or drostanolone propionate (2 α -methyl-dihydrotestosterone propionate) and were sacrificed at various intervals after institution of the diet. Although the first hepatoma was observed only after a latent period of 146 days, androsterone potentiated the growth of DAB-induced hepatomas. Multiple tumors were found in five of the ten rats and one animal, sacrificed after 188 days, had peritoneal metastases. Neither retrotestosterone nor testosterone had any effect on hepatoma development, while both drostanolone propionate and androsterone plus sodium sulfate inhibited development of DAB-induced hepatomas.

0116 REGULATION OF RECEPTORS FOR ESTROGENS IN MAMMARY TUMORS: *IN VIVO* EFFECT OF PROLACTIN. (Fr.) Vignon, F. (Inst. Biol., Montpellier, France) and H. Rochefort. *C R Acad Sci (Paris)* 278(1):103-106, 1974.

Mammary tumors were induced in female Sprague-Dawley rats by administration of 20 mg 7,12-dimethylbenz-(a)anthracene (DMBA; route unspecified). Rats whose tumors regressed after oophorectomy were given sheep or rat prolactin (1 mg/day s.c. for 5 days) or physiological saline. The binding of estradiol by receptors in tumor extracts, cytosol, and the uterus were studied *in vitro*. After oophorectomy a rapid exponential decrease occurred in the number of moles of estradiol which were bound per mg protein. Administration of rat or ovine prolactin had no effect on this decrease. These findings suggest that estradiol probably increases the concentration of its own receptors in mammary tumors while stimulating secretion of prolactin by a positive feed-back mechanism.

0117 SKIN TRANSPLANTATION FOR THE STUDY OF CHEMICAL CARCINOGENESIS IN MOUSE SKIN. I. SKIN TRANSPLANTATION ON THE DORSAL FASCIA OR PANNICULUS CARNOSUS. (Ger.) Worst, P. K. M. (German Cancer Res. Ctr., Heidelberg), R. Bauz, U. Wahn and E. Knauer. *Z Krebsforsch* 80(4):307-316, 1973.

Two techniques have been developed for transplantation of mouse skin. Mouse strains C3H, C57B1/10, B10D2, B10LP, C57B1/6, A/JA, BALB/c and AKR were employed. Transplants were performed only on mice whose hair was in the telogenic phase. The first technique, which is best suited for transplanting carcinogen-treated skin, consists in placing large grafts directly on the dorsal fascia and fastening them with Michel wound clips. Mortality during and after surgery was less than 5%. The best results (95% success) were obtained with male and female C3H mice, aged 60-70 days; the success rates were lower in mice aged 110-120 days. Good results were also obtained with AKR, A/JA and BALB/c mice. The second technique, which consists of applying small grafts to the panniculus carnosus and covering them with a small adhesive bandage clipped to the skin on the back, is especially suitable for allografting since rejection occurred almost simultaneously in all animals. The good results obtained with these techniques are attributed to the methods of fastening the grafts. Grafts were fastened for periods as short as possible (1 day for large grafts and 4-5 days for small grafts).

0118 BIOLOGICALLY ACTIVE COMPOUNDS FROM EUPHORBIAEAE. I. SKIN IRRITANTS AND COCARCINOGENS FROM *EUPHORBIA COOPERI* N.E.Br. (Ger.) Gschwendt, M. (German Cancer Res. Ctr., Heidelberg) and E. Hecker. *Z Krebsforsch* 80(4):335-350, 1973.

A di- and a triester of 12-deoxy-16-hydroxyphorbol (I) were isolated from *Euphorbia cooperi*. The diester (II) has an angelic acid radical on carbon 13 and an isobutyric acid radical on carbon 16 of the parent compound, while the triester (III) is a 20-acetate of the diester. Compounds II and III were tested for their skin irritant and cocarcinogenic activity along with two semisynthetic analogues, 13-O-[2-methyl-2-*cis*-butenoyl]-16-O-decanoyl-12-deoxy-16-hydroxyphorbol (IV) and 13-O-[2-methyl-2-*cis*-butenoyl]-16-O-tetradecanoyl-12-deoxy-16-hydroxyphorbol (V). In tests on the ears of mice, compounds II and III were less active skin irritants than croton oil factor A₁, while compounds IV and V had irritant activities comparable to A₁. In standardized cocarcinogen tests performed on mouse skin, compounds II, III, V, factor A₁, and an acetone extract of *Euphorbia* latex were applied twice a week for 36 or 48 wk using 7,12-dimethylbenz(a)anthracene (DMBA) as an initiator. Compounds II, III, and V were much weaker cocarcinogens than croton oil factor A₁. In addition to many papillomas, A₁ and DMBA induced two squamous cell carcinomas and two basal cell carcinomas, while compounds II, III, and the acetone extract of *E. cooperi* latex induced no malignant tumors. It is suggested that the low cocarcinogenic activity of II and III is due to the absence of a long-chain fatty acid in the side chain.

0119 THE INFLUENCE OF HIBERNATION UPON THE CARCINOGENIC EFFECT OF N-DIETHYLNITROSAMINE IN EUROPEAN HAMSTERS. (E.) Mohr, U. (Med. Coll., Hannover, Germany), J. Althoff, R. Spielhoff and H. Bresch. *Z Krebsforsch* 80(4):285-288, 1973.

N-diethylnitrosamine (DEN) was administered s.c. to 120 wild European hamsters of both sexes. Half of the animals were then maintained under conditions conducive to hibernation while the others were maintained under standard laboratory conditions; the injections of DEN were continued on a weekly basis throughout the 5 months of hibernation. Within 7 wk, 80% of the nonhibernating males developed tumors of the nasal and paranasal cavities; similar tumors were seen in 53% of the females after 13 wk. In addition, tracheal tumors were found in 67% of the males and 43% of the females, lung tumors were seen in 53% of the males and 37% of the females, and tumors of the forestomach were seen in 30% of the animals of both sexes. Among the hibernating animals, tumors of the nasal and paranasal cavities developed after 17 wk in the males and after 12 wk in the females. Tracheal papillomas were found in 57% of the males and 37% of the females, pulmonary tumors were found in 43% of the males and 33% of the females, and forestomach papillomas were seen in 30% of the males and 23% of the females. The survival rate of the hibernating animals was higher than that of the nonhibernating animals.

0120 ASBESTOS-INDUCED INTRATHORACIC TISSUE REACTIONS. (E.) Gross, P. (Industrial Hlth. Fdn., Inc., Pittsburgh, Pa.) and R. A. Harley, Jr. *Arch Pathol* 96(4):245-250, 1973.

Male rats and hamsters were injected intrapleurally with chrysotile, amosite, and crocidolite asbestos dusts which had been hammer-milled (to coat the asbestos with nickel-containing alloy), treated with *aqua regia* (to remove trace metals), heated and treated, heated, or rendered metal free. Most of the rats developed differentiated malignant chest tumors which were classified as fibrosarcomas (25), mesotheliomas (4), rhabdomyosarcomas (3), osteogenic sarcomas (2), and fibroliposarcomas (1). Most of the hamsters developed undifferentiated chest tumors. The heated asbestos dusts induced only 1/10 as many tumors as the untreated dusts. There were no differences in the number of tumors induced by the metal free dusts and the dusts to which metals had been added. Thus, these data do not support the trace-metal hypothesis for the mechanisms of asbestos-induced cancer.

0121 INDUCTION OF ARYL HYDROCARBON HYDROXYLASE IN HUMAN LYMPHOCYTES AND PULMONARY ALVEOLAR MACROPHAGES - A COMPARISON. (E.) Cantrell, E. (M.D. Anderson Hosp. Tumor Inst., Houston, Texas), D. Bushbee, G. Warr and R. Martin. *Life Sci* 13(12):1649-1654, 1973.

Exposure of animals to cigarette smoke causes an increase in the levels of aryl hydrocarbon hydroxylase (AHH) in various tissues. The innate capacity for enzyme induction is genetically determined but the extent of induction and AHH levels in various tissues may vary. AHH levels in human pulmonary alveolar macrophages (PAMs) were determined, as was the AHH induction of cultured lymphocytes from matched volunteers. The induction of cultured lymphocytes by 3-methylcholanthrene was similar in smokers and nonsmokers, ranging from a 0.2 - 4.2 fold induction. AHH levels in nonsmoker PAMs were 0 - 0.020 U and in smokers were 0.032 - 0.253 U. The correlation of AHH activity in PAMs with lymphocyte inducibility was significant in both nonsmokers and smokers. The slope of the line of regression relating AHH in PAMs to AHH inducibility in lymphocytes was 8.5 fold higher in smokers than nonsmokers, reflecting the induction of AHH in PAMs by smoking.

0122 STRUCTURE OF A COMPLEX RESULTING FROM THE ACTION OF A POLYCYCLIC AROMATIC EPOXIDE ON A DEOXYRIBONUCLEIC ACID. (Fr.) Daudel, P. (Radium Inst., Paris, France), M. Croisy-Delcey, P. Jacquignon and P. Vigny. *C R Acad Sci (Paris)* 277: 2437-2438, 1973.

Calf thymus DNA (11 mg in 11 ml triply distilled water) was incubated for 2 hr at 37 C with 4,6-epoxy-5,6-dihydro-7-methylbenz(a)anthracene (500 µg in 0.2 ml acetone). After allowing the solution to cool and extracting three times with 12 ml ether, 200 mg NaCl and 10 ml absolute ethanol were added to 5 ml of the aqueous phase. DNA was agitated with alcohol for 72 hr, dried, dissolved in pH 7.4 Tris buffer

and dialyzed against a $10^{-2}M$ solution of Tris and NaCl. Two more samples of DNA were treated in the same manner but (1) without incubating with the epoxide and (2) incubating with 5,6-dihydroxy-5,6-dihydro-7-methylbenz(a)anthracene. The fluorescent spectrum of the DNA-epoxide complex differed from those of naphthalene and 7-methylbenz(a)anthracene, ruling out the possibility that the C_5-C_6 bond of the epoxide is opened or that the $C_5=C_6$ double bond is reestablished. Fluorescent spectra for the epoxide-DNA complex and for the dihydroxydihydro derivative of 7-methylbenz(a)anthracene were superimposable, but the vibrational structure was less pronounced for the epoxide complex, probably due to the presence of DNA. It is concluded that the epoxide-DNA complex and the dihydroxydihydro derivative must contain the same "delocalized system". Other findings have revealed that the complex, which is formed by a very strong bond, probably chemical in nature, consists of one molecule of 7-methylbenz(a)anthracene and a population of 20,000 to 30,000 nucleotides.

0123 ENHANCED PRODUCTION OF α -FETOPROTEIN IN HEPATOCARCINOGENESIS OF RATS PRENATALLY EXPOSED TO DIETHYLNITROSOAMINE. (E.) Kitagawa, T. (Dept. Path., Cancer Inst., Tokyo, Japan) and H. Sugano. *Gann* 64(6):645-646, 1973.

Pregnant Donryu rats were injected i.p. with diethylnitrosoamine (DEN). Their offspring were maintained on a basal diet for 8 weeks, after which they and a group of control animals of the same age were given drinking water containing 50 ppm DEN. In the experimental group, α -fetoprotein was detected in some of the sera after 9 weeks on the DEN treatment; it was present in the sera of nearly all of these animals after 18 weeks. In the control group, α -fetoprotein was first detected after 12 weeks and was present in a majority of the animals after 15 weeks. Thus, the prenatal administration of DEN markedly enhanced the postnatal carcinogenicity of the compound; this effect was particularly marked among the females. The liver cell islands of the prenatally treated animals contained normal amounts of adenosine triphosphatase and glucose-6-phosphatase prior to the commencement of the postnatal DEN treatment.

0124 CELL PROLIFERATION, RNA AND PROTEIN SYNTHESIS DURING CARCINOGENESIS IN THE RAT LIVER. (E.) Stöcker, E. (Inst. Path., U. Würzburg, Germany), H. K. Wullstein, K.-H. Friederichs and C. Friederichs. *Beitr Pathol* 150(2):188-196, 1973.

Forty-five young adult male Sprague-Dawley rats received N-nitrosomorpholine (NNM) continuously over a period of 7, 15, 43, 69, 118, 164, or 218 days (12 mg/% solution in the drinking water). Autoradiographic experiments were performed after a single injection of either 3H -thymidine or 3H -cytidine and 3H -phenylalanine to study nucleic acids and protein-synthesis in liver cells. The percentage of DNA-synthesizing nuclei is elevated in cells of type A (reversible altered) from 7 up to 69 days, from 118 days in cells of type B (glycogen storage), and after 164 days in cells of type C (hepatoma cells). A commutation from the slow to the rapid mode of cell

proliferation can be observed when the 3H -thymidine labelling index reaches high values. RNA- and protein-synthesis (164 days after a continuous application of NNM) occur in proportion to the enlargement of the nucleolus, the karyoplasm, and the cytoplasm as compared to the corresponding controls. The enhanced synthesis of RNA and protein, especially in the enlarged cells of type B, was interpreted as a consequence of a functional swelling of these cell compartments or, with respect to the nucleus in some cases, as due to polyploidization. The ratio of amino acid incorporation in the cytoplasm to that in the nucleus was somewhat lower in tumor cells than in controls. However, this phenomenon was not specific for tumor cells since it was observed also in hepatocytes after partial hepatectomy and in other conditions not associated with carcinogenesis. It appeared that under the test conditions employed no significant differences in cellular RNA and protein synthesis can be seen between normal, preneoplastic and and tumorous liver epithelia.

0125 LYMPHOMAS IN BALB/c MICE INOCULATED WITH SUPERNATANTS FROM CHEMICALLY INDUCED SARCOMAS. (E.) Basombrio, M. A. (Inst. Cancer Res., Phila., Pa.). *J Natl Cancer Inst* 51(4):1157-1162, 1973.

To determine if acellular extracts from primary sarcomas induced by 3-methylcholanthrene (MCA) could be oncogenic, BALB/c mice were inoculated with supernatants from these tumors. A single inoculation at birth raised the incidence of lymphoid neoplasms from 7 to 45% at 18 months. The increase was remarkable (0-100% at 18 months) when fresh tumor supernatants were repeatedly injected into young mice. These results could not be matched by replacing tumor tissue by normal, regenerating, embryonic, or necrotic tissues in control procedures. Similar results were not obtained with different mouse strains and tumor filtrates instead of supernatants. These findings, obtained under conditions which excluded cell transplantation or transfer of chemical carcinogen, indicated that primary MCA tumors contained a nascent murine leukemia virus (MuLV) to which BALB/c mice were susceptible. To confirm this assumption, several individual MCA tumors and normal tissues were tested for the presence of MuLV with the XC syncytium assay. Virus activity was detected in 6 of 14 individual tumors, in 1 of 7 tissue samples from normal mice, and in 2 of 8 normal tissue samples from tumor-bearing mice. Titers were higher in tumors. Although nascent MuLV was more likely to be found in MCA tumors than in normal tissues, it could not be ascertained whether its presence was necessary or accidental in chemical oncogenesis.

0126 EVALUATION OF DIMETHYLHYDRAZINE INDUCED TUMOURS IN MICE AS A MODEL SYSTEM FOR COLORECTAL CANCER. (E.) Haase, P. (Sch. Med., Leeds 2, England), D. M. Cowen, J. C. Knowles and E. H. Cooper. *Br J Cancer* 28(6):530-543, 1973.

Male and female NMRI mice were given 14 to 30 weekly s.c. injections of 1,2-dimethylhydrazine dihydrochloride solution (DMH). The drug treat-

ment produced tumors of the colon and anal region, the former being found in 100% of the treated mice after 22 wk and the latter being found in 5% of the animals. After 4 wk of injections, the liver always showed signs of toxic damage. Among the animals given 14 or 17 weekly doses of DMH, 90% of the females and 83% of the males developed tumors of the colon; the number of tumors found in individual animals was less than that seen after 22 or more weekly injections. Ultrastructurally, the DMH induced tumors resembled human colonic carcinomas and the tumors induced in rats by treatment with 3-2'-dimethyl-4-aminobiphenol. The data indicate that dimethylhydrazine or a derivative of it brings about a field change in the mucosa of the colon which makes it more susceptible to tumor formation. The data further suggest that the adenomas which were formed after relatively few DMH injections were the forerunners of the carcinomas which were found in animals given 30 or more weekly injections.

0127 EFFECT OF N-HYDROXY URETHAN ON NUCLEIC ACID BIOSYNTHESIS IN SWISS MICE. (E.)

Ranadive, D. V. (Cancer Res. Inst., Tata Mem. Ctr., Bombay, India), K. N. Arjungi and S. V. Bhide. *Indian J Cancer* 10(3):333-337, 1973.

Chemically induced fibrosarcomas were transplanted into adult Swiss mice which, along with untreated adults and newborns, were then injected with N-hydroxy urethan or urethan. The animals were then injected with ^{32}P labeled orthophosphate or C^{14} labeled phenylalanine. N-hydroxy urethan significantly inhibited DNA and RNA biosynthesis in the newborn mice, with the rate returning to normal 7 days postinjection. Nucleic acid biosynthesis was also inhibited in the tumor tissues of the adult tumor-bearing mice, but the rate returned to normal within 48 hr. N-hydroxy urethan did not inhibit nucleic acid biosynthesis in the lung, liver, or kidney tissues of the nontumor-bearing adult mice. Neither urethan nor N-hydroxy urethan had any effect on protein biosynthesis in the newborn animals. N-hydroxy urethan exerted a greater inhibitor influence on nucleic acid biosynthesis in the neonates than did urethan, although the inhibitory effect of urethan lasted as long as that of N-hydroxy urethan.

0128 FORMATION OF N⁷-METHYLGUANINE IN NUCLEAR DNA AND CYTOPLASMIC RNA IN MICE ON CONTINUOUS ORAL ADMINISTRATION OF DIMETHYLNITROSAMINE- ^3H SOLUTION. (E.) Nemoto, N. (Cancer Inst., Tokyo, Japan) and S. Takayama. *Z Krebsforsch* 80(2):113-125, 1973.

Dimethylnitrosamine- ^3H (DMN- ^3H) solution was administered *ad libitum* to male ICR/JCL mice in their drinking water. After 1, 2, 3, 5, 7, 10, 14, 21, or 30 days of this treatment, the animals were killed and their livers, lungs, kidneys, and pancreases examined for the formation of N⁷-methylguanine in the nucleic acids. The liver nucleic acids were preferentially labelled during the first week, with their radioactivity then decreasing

slightly after 3 wk. The radioactivity of the nucleic acids in the lungs and kidneys gradually increased, nearly reaching the level of the liver nucleic acids after 30 days. However, the amount of N⁷-methylguanine in the nucleic acids of the liver was 2 to 4 times that in the nucleic acids of the lungs and kidneys after 30 days. The maximal level of N⁷-methylguanine in DNA was found after 21 days, when approximately 0.1% of guanine residues in the liver DNA were methylated. Maximal methylation of RNA was also observed after 21 days. Initially, the methylation of low molecular weight transfer RNA of the liver was greater than that of ribosomal RNA of the liver, but later the extents of methylation to the different cytoplasmic RNA species became similar. Since these findings conflict with those of other investigators, who found with labelled 2-acetylaminofluorene a correlation between carcinogenesis and binding of carcinogen to ribosomal RNA, it appears that the significance of the binding of carcinogens to cellular macromolecules under conditions inducing tumors should be re-evaluated.

0129 SOME OBSERVATIONS ON THE DISTRIBUTION OF TRACE METALS IN CHRYSOTILE ASBESTOS.

(E.) Morgan, A. (Hlth. Physics Med. Div., Atomic Energy Res. Establishment, Harwell, Didcot, Berks, Great Britain), A. E. Lally and A. Holmes. *Ann Occup Hyg* 16(3):231-240, 1973.

The distribution of iron, chromium, nickel, cobalt, and scandium in a number of samples of chrysotile asbestos was investigated. The data indicated that the distribution of trace metals in commercial chrysotile asbestos samples is complex. The metals examined can all be present as isomorphous substitutes for magnesium in the octahedral layer of the chrysotile fibril, and scandium appears to be almost uniquely present in this form. In samples which contained few associated mineral impurities, most of the other trace metals were contained in the brucite layer. In most samples, however, trace metals were also present in associated minerals and alloys, some of which were relatively insoluble (magnetite and chromite) and others of which were relatively soluble with reference to structural magnesium. In general, the concentration of most of the trace metals was much greater in the mineral and alloy impurities associated with chrysotile than in the fiber itself.

0130 CERVICAL CARCINOMA AND CARCINOMA *IN SITU* ASSOCIATED WITH ORAL CONTRACEPTIVES. (Ger.)

Wunder, G. (Municipal Clinic Obstet. Gynecol., Ludwigshafen/Rhein, Germany). *Fortschr Med* 91(27):1082-1084, 1973.

Papanicolaou smears and questionnaires were made to study possible relationships between cervical cancer (carcinoma and carcinoma *in situ*) and oral contraceptives in 21,642 women, aged 20-45 yr, who had given birth. The overall prevalence of cervical cancer was the same (0.48%) among those who had taken oral contraceptives (8199 women) and controls (13,443 women). In contrast to previously reported studies, the prevalence of cervical cancer in women aged 35-

40 yr was lower (0.39%) among those who had taken oral contraceptives than among controls (0.57%). Since some of the controls may not have reported that they had taken oral contraceptives, data obtained for this age group were not included with those obtained for younger women. In younger women (20-35 yr) the prevalence of cervical cancer was 0.23% higher among those who had taken oral contraceptives than among controls. However, these data cannot be interpreted to mean that there is a causal relationship between cervical cancer and oral contraceptives since other factors (time at which sexual intercourse was begun, number of sex partners, parity, social status and race) are also related to the development of cervical cancer. Large-scale prospective studies to determine incidence rates are needed to prove the existence of such a relationship.

0131 ESTABLISHMENT AND CHARACTERIZATION OF A TRANSPLANTABLE DIBUTYLNITROSAMINE-INDUCED MOUSE BLADDER TUMOR LINE FCB. (E.) Flaks, A. (Sch. Med., U. Leeds, England) and B. Flaks. *Cancer Res* 33(12):3285-3292, 1973.

Male (IF x C57BL) F₁ hybrid mice were given 18 s.c. injections of dibutyl nitrosamine (DBN). Three wk after the final injection, their bladders were removed and implanted s.c. into the flanks of six syngeneic animals. Three of the implanted bladders gave rise to tumors, two malignant transitional cell carcinomas and a hemangioma. All of the tumors were transplanted s.c. into the flanks of additional (IF x C57BL)F₁ mice. One of the transitional cell carcinomas, designated FCB, has been serially transplanted for 42 generations and has been shown by light and electron microscopy to be a rapidly growing tumor with a stable morphology. The tumor will grow in a variety of sites in either C57BL or IF mice. It will grow rapidly *in vitro* as a monolayer and reforms solid tumor tissue upon reimplantation. The growth characteristics and morphology of the FCB tumor are discussed.

0132 CHANGES IN PRODUCTION OF GONADOTROPIC HORMONES AND ANDROGENS DURING EXPERIMENTAL REPRODUCTION OF TUMORS OF THE TESTIS. (E.) Dmitriev, V. N. (Izhevsk Med. Inst., USSR). *Bull Exp Biol Med* 76(8):974-976, 1973.

Dimethylbenzanthracene (DMBA), methylcholanthrene (MC), or astringent emulsions of zinc and copper sulfates were injected into the right testis of sexually mature rats and guinea pigs. The injections usually led to atrophy and deformation of the treated testis; in addition, the MC and DMBA injections produced teratomas and sarcomas in the testes of a small percentage of the animals. In the animals showing precancerous and cancerous changes in the testis, there was some increase in the pituitary levels of FSH and LH and in the urinary 17-ketosteroid levels. These changes occurred several weeks before the appearance of the first tumors. In a second experiment, cryptorchid animals were injected with testosterone propionate and astringent emulsions. Cryptorchidism was accompanied by testicular atrophy, increases in the pituitary FSH and LH levels and the

urinary 17-ketosteroid levels, and, in one case, tumor development. Similar results were obtained when the animals were treated with hormones and the astringent emulsions. Thus, the development of testicular tumors is accompanied by an increase in the production of gonadotropins and androgens.

0133 PHOTOCHEMICAL BINDING OF ANTHRACENE AND OTHER AROMATIC HYDROCARBONS TO DEOXYRIBONUCLEIC ACID WITH ATTENDANT LOSS OF TRITIUM. (E.) Blackburn, G. M. (Dept. Chem., The U., Sheffield, Great Britain), J. Buckingham, R. G. Fenwick, P. Taussig and M. H. Thompson. *J Chem Soc (Perkin I)* 1(22):2809-2813, 1973.

Anthracene was bound covalently to calf thymus DNA by means of long-wavelength UV irradiation to a greater extent than were benzo(e)pyrene, benzo(a)pyrene, dibenz(a,c)anthracene, 3-methylcholanthrene, 7,12-dimethylbenz(a)anthracene, benz(a)anthracene, or dibenz(a,h)anthracene. ³H was incorporated into the photochemical product resulting from the irradiation of doubly labeled hydrocarbons and DNA to a lesser extent than was ¹⁴C. In the case of anthracene, the ratio of incorporation of the two isotopes was ca. 3:4, which was independent of the extent of irradiation or of hydrocarbon binding. The data suggest that the mechanism of action involved in the bonding of hydrocarbons to DNA is an aromatic substitution process of the same kind as that involved in the formation of photoproducts between benzo(a)pyrene and 1-methylcytosine and benzo(a)pyrene and thymine. The data further suggest that the carcinogenicity of polycyclic aromatic hydrocarbons is associated with their potential for cross-linking DNA rather than with their capacity for simple covalent binding to DNA.

0134 COMPARATIVE METABOLISM OF 7,12-DIMETHYLBENZ(a)ANTHRACENE IN LIVER AND MAMMARY TISSUE. (E.) Tamulski, T. S. (Roswell Pk. Mem. Inst., Buffalo, N.Y.), C. E. Morreal and T. L. Dao. *Cancer Res* 33(12):3117-3122, 1973.

The livers and mammary glands of female Sprague-Dawley rats were homogenized, and the supernatants from the homogenates were incubated with a reaction mixture containing 7,12-dimethylbenz(a)anthracene (DMBA). The metabolism of DMBA to its hydroxymethyl derivatives differed in the hepatic and mammary tissue homogenates. Countercurrent distribution and carrier recrystallization were effective additional tools in the identification of 7-hydroxymethyl-12-methylbenz(a)anthracene, 12-hydroxymethyl-7-methylbenz(a)anthracene, and 7,12-dihydroxymethylbenz(a)anthracene. In the hepatic tissue, DMBA was transformed into all three of these metabolites, whereas only the monohydroxy compounds were formed in the mammary gland homogenate. Pretreatment of the rats with 3-methylcholanthrene induced a marked increase in the DMBA-metabolizing enzymes in the liver, thus leading to further conversion of the hydroxymethyl derivatives to more polar components. In contrast, the mammary gland homogenates produced a smaller amount of 7-hydroxymethyl-12-methylbenz(a)anthracene

and a larger amount of 12-hydroxymethyl-7-methylbenz(a)-anthracene. The data illustrate, for the first time, the ability of mammary tissue to metabolize 7,12-dimethylbenz(a)anthracene.

- 0135 CHROMOSOMAL ABERRATIONS AND CARCINOGENESIS BY VARIOUS BENZ(a)ANTHRACENE DERIVATIVES. (E.) Sugiyama, T. (Kobe U. Sch. Med., Japan). *Cann* 64(6):637-639, 1973.

Chromosomes obtained from the femur bone marrow of male Long-Evans rats which had been injected i.v. with lipid emulsions of various benz(a)anthracene derivatives were examined for aberrations and the results correlated with the rate of fibrosarcoma incidence following the i.m. injection of 2.5 mg of each benz(a)anthracene compound. The chromosome-damaging capacity was dependent upon the chemical structure of the compound in question. When the median of the percentage of aberrant metaphase cells at 12 and 24 hr post-injection was used to indicate the chromosome-damaging capacity of each chemical, a clear correlation between this capacity and carcinogenicity was found. Thus, chromosomal damage may play an important role in carcinogenesis. This may be due to the effects of the genetic rearrangement of specific chromosomal regions during chromosome breakage.

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- 0198 INDUCTION OF LOCAL DENATURATION IN DNA *IN VITRO* BY PHLEOMYCIN AND CAFFEINE. (E.) Sleight, M. J. (C.S.I.R.O. Div. Anim. Genet., Epping, Australia) and G. W. Grigg. *FEBS Lett* 39(1):35-38, 1974.
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- 0200 ULTRASTRUCTURE OF HUMAN MESOTHELIOMAS. (E.) Davis, J. M. G. (Inst. Occupational Med., Edinburgh, Scotland). *J Natl Cancer Inst* 52(6):1715-1752, 1974.
- 0201 LIVER TUMOURS AND STEROID HORMONES. (E.) Cattani, D. (Creteil U. Sch. Med., Villeneuve St. Georges, France), P. Vesin, J. Wautier, R. Kalifat and S. Meignan. *Lancet* (7862):878, 1974.
- 0202 FLUORESCENCE STUDY OF THE INTERACTION OF 3,4-BENZOPYRENE WITH MICROSOMAL MEMBRANES. (E.) Ibbetson, A. L. (Biol. Lab., U. Kent, Canterbury, England) and R. B. Freedman. *Biochem Soc Trans* 2(2):343-345, 1974.
- 0203 THIOACETAMIDE LOWERING OF LIVER GLUCOSE. (E.) Vann, L. S. (Arequipa Fdn., Palo Alto, Calif.). *Proc West Pharmacol Soc* 17:244-246, 1974.
- 0204 ON THE EFFECT OF ORTHO-TOLIDINE ON BENZIDINE INDUCTION OF TUMORS IN RATS. (Rus.) Pliss, G. B. (N. N. Petrov Res. Inst. Oncol., Leningrad, USSR) and N. I. Volifson. *Vopr Onkol* 20(2):53-58, 1974.
- 0205 HORMONE PROMOTES BREAST CANCER. (E.) Anonymous. *Chem Eng News* 52(14):22, 1974.
- 0206 PHOSPHOLIPIDS OF RAT LIVER IN DYNAMICS OF CHEMICAL CARCINOGENESIS. (Rus.) Blagorodov, S. G., (State Res. Inst. Oncol., Rostovon-Don, USSR), V. M. Polyakov, A. V. Arkhangelskaya and M. M. Petyaev. *Vopr Med Khim* 19(3):305-307, 1973.
- 0207 INVESTIGATION OF FREE RADICAL PROCESSES IN RAT LIVER ORGANELLES UNDER CHEMICAL CARCINOGENESIS. (Rus.) Kotrikadze, N. K. (Tbilisi State U., USSR), B. A. Lomsadze and M. A. Tsartsidze. *Biofizika* 19(2):304-307, 1974.
- 0208 ISOLATION AND IDENTIFICATION OF THE CARCINOGEN N-HYDROXY-2-FLUORENYLACETAMIDE AND RELATED COMPOUNDS BY LIQUID CHROMATOGRAPHY. (E.) Gutmann, H. R. (VA Hosp., Minneapolis, Minn.). *Anal Biochem* 58(2):469-478, 1974.
- 0209 THE HISTOLOGICAL PICTURE OF ENDOMETRIUM-MATERIAL FOLLOWING PROLONGED USE OF ORAL CONTRACEPTIVES. (E.) Varadi, I. (Weil Emil Hosp., Budapest, Hungary) and M. Scholz. *Acta Morphol Acad Sci Hung Suppl* 17:119, 1973.

See also:

- * (Rev): 0004, 0005, 0008, 0009, 0011, 0015, 0016, 0019, 0020, 0025, 0033, 0046, 0049, 0050, 0054, 0055
- * (Viral): 0336
- * (Immun): 0365, 0368, 0378, 0389, 0396, 0400, 0415
- * (Epid-Biom): 0495

- 0210 TOXICITY OF ^{90}Sr - ^{90}Y IN CHINESE HAMSTERS. (E.) Brooks, A. L. (Inhalation Toxicol. Res. Inst., Albuquerque, N. M.), S. A. Benjamin and R. O. McClellan. *Radiat Res* 57(3):471-481, 1974.

Strontium-90 citrate was injected i.p. into Chinese hamsters at activity levels of 0.2, 0.5, 1.0, 2.0, 3.0, and 5.0 $\mu\text{Ci/g}$ body weight. The animals were held for lifespan observation. Control hamsters were injected with sodium citrate. The lifespan of all ^{90}Sr -treated animals was shortened, with the severest shortening occurring in those receiving the highest ^{90}Sr doses. Animals receiving 3.0 or 5.0 $\mu\text{Ci/g}$ died within the first 2 weeks. Those in other activity level groups had 50% survival rates at 90 days after 2.0 $\mu\text{Ci/g}$, 260 days at 1.0 $\mu\text{Ci/g}$, 700 days at 0.5 $\mu\text{Ci/g}$, 900 days at 2.0 $\mu\text{Ci/g}$ and 1100 days for controls. Three osteosarcomas were found, all in animals injected with 1.0 $\mu\text{Ci/g}$, which is a level of activity known to produce a high incidence of bone tumors in the mouse. These results suggest that the Chinese hamster is more resistant to bone tumor induction than is the mouse. A high incidence of myeloproliferative disorders was found both in older control and in ^{90}Sr -injected animals. The obvious result of species differences in response to ^{90}Sr adds caution to extrapolations of data from one animal species to man. It is suggested that the late occurrence and high incidence of myeloproliferative disorders may provide a model for studying the effects of various stresses in altering frequency or temporal sequence of their occurrence.

- 0211 OSTEOSARCOMA OF THE PELVIS FOLLOWING RADIOTHERAPY FOR CARCINOMA OF THE CERVIX. (E.) Rushforth, G. F. (Royal Natl. Orthopaedic Hosp. Stanmore, Great Britain). *Br J Radiol* 47(554): 149-152, 1974.

A 54-year-old woman was referred for orthopedic care with a 2-year history of increasing pain in both hips. Ten years previously biopsy of the cervix had shown anaplastic squamous cell carcinoma with deep infiltration. The patient was at that time treated with three insertions of intrauterine and intravaginal radium, after which supplementary external irradiation (2300-2600 rads) was also given. On referral for orthopedic care, the patient was treated with high femoral osteotomy with internal fixation on both sides; this treatment gave considerable relief from pain for 5 years. The return of pain was then treated with total hip replacement on both sides. Within 1 month, increasing pain and loss of movement returned to the right side. Biopsy of surrounding bone of the acetabulum revealed osteosarcoma with no evidence of infection. The patient succumbed to the disease 5 years later. Any patients previously treated with radiotherapy and later suspected of having radiation osteitis should be considered at risk of developing osteosarcoma.

- 0212 PLUTONIUM CANCER WARNING SPELLS TROUBLE FOR BREEDER. (E.) Anonymous. *New Sci* 61(887): 542, 1974.

Radioactive plutonium appears significantly different

from other radioactive elements. It is alleged that a single particle can cause lung cancer and the chemical has an unusually long half-life, 24,400 yr. Once taken into the lung, it apparently remains lodged there permanently. Therefore, while one particle of PuO_2 gives a dose of only .0003 rem/yr averaged over the whole lung; it gives 4000 rem/yr to the tissue actually irradiated. For the lung, the maximum dose for people working in the nuclear industry is 15 rem/yr, which is estimated to cause one case of cancer/33,000 workers/yr. It was estimated that a single particle of PuO_2 lodged in the lung has one chance in 2000 of actually causing cancer. It is argued that to meet current safety standards, the release of plutonium should be reduced by a factor of 115,000. The major use of plutonium thus far has been military. However, it can also be used as a reactor fuel. A large number of plutonium reactors would result in a large amount of transportation and reprocessing of plutonium, with the inherent dangers of leakage and accident. Of 25 persons exposed to a plutonium fire in 1965, 1 took at least 137,000 hot plutonium particles into his lungs and the others inhaled 12,500. As yet no cases of cancer have developed from these exposures.

- 0213 UNSCHEDULED DNA SYNTHESIS AFTER ULTRAVIOLET MICROIRRADIATION OF THE CELL NUCLEUS. (E.) Moreno, G. (Inst. Cellular Path. Bicetre Hosp., France) and C. Salet. *Radiat Res* 58(1):52-59, 1974.

Xeroderma pigmentosum (XP) fibroblasts and KB cells in tissue culture were microirradiated over one or more nuclear areas 5 mm in diameter with UV doses of 10, 100, 1000 and 2000 ergs/mm². Following irradiation, the cells were labeled with ^3H -thymidine ($^3\text{HTdR}$) for 3 hours and autoradiographed. XP cells not in the S phase did not take up $^3\text{HTdR}$, while in the KB cells, an incorporation localized over the irradiated area(s) of the nucleus was observed. XP and KB cells in the S phase which had been microirradiated with 10 or 100 ergs/mm² were labeled throughout the nucleus, but cells which had been irradiated with 1000 ergs/mm² showed a lower incorporation in the irradiated area(s) than in the non-irradiated portion of the nucleus. When the irradiated area of the KB cell nucleus was increased by irradiating two or four spots with the same UV dose, the average number of grains per irradiated area decreased. No modification of the unscheduled DNA synthesis was detected after partial irradiation of the cytoplasm.

- 0214 PREVIOUS RADIATION EXPOSURE IN PATIENTS WITH LEUKEMIA. (E.) Rodriguez, V. (M. D. Anderson Hosp., Houston, Texas), G. P. Bodey, J. M. Trujillo and E. J. Freireich. *Arch Intern Med* 132: 874-877, 1973.

Of 423 adults with acute (356 cases) or chronic (67) leukemia admitted between 1966 and 1971, 23 (5.4%) had received prior radiation exposure. Of these 23, 19 had acute leukemia and 4 had chronic leukemia. Sixteen had acute myelogenous leukemia (3 of them, erythroleukemia), 3 had acute undifferentiated leukemia, 2 had chronic myelogenous leukemia in blastic phase, and 2 had chronic lymphocytic leukemia

for which no previous connection to radiation therapy has been established. Three patients were occupationally exposed to radiation, 14 had received therapeutic radiation for malignant diseases, and six for nonmalignant diseases. Those who were occupationally exposed probably with a low but sustained dose, had a median duration of 20 yr from time of exposure to leukemia diagnosis. Those receiving therapy for nonmalignant diseases (presumably low doses) had 10 yr and those receiving high doses for malignant diseases therapy, 6 yr. In the 16 patients for whom cytogenetic studies were available, 9 had structural alteration and damage in bone marrow cells and/or phytohemmagglutinin-stimulated peripheral blood. Additional factors which may have contributed to leukemia development in these patients were the treatment of one patient with propylthiouracil for longer than 2 years after having received ^{131}I , and the use of alkylating agents alone or in combination with prednisone for more than 2 yr in 4 other patients. The annual incidence of radiation exposure among the patients in this study was 6% during 1966 through 1968, 3% during 1969 and 1970, and 10% during 1971. The frequency of previous radiation exposure in patients with leukemia increased substantially during the last year of this study.

0215 CHROMOSOME BREAKAGE IN HUMAN PERIPHERAL LYMPHOCYTES AFTER RADIOACTIVE IODINE (^{125}I) TREATMENT. (E.) Boyd, E. (Royal Hosp. Sick Children, Glasgow, Scotland), M. A. Ferguson-Smith, I. R. McDougall and W. R. Grieg. *Radiat Res* 57(3):482-487, 1974.

The use of ^{125}I (half-life of 60 days) vs ^{131}I (half-life 8 days) in treatment of thyrotoxicosis prompted a study of possible undesirable extrathyroidal radiation damage. Five female patients (aged 51-69) who had previously received ^{125}I (15-40 mCi) for thyrotoxicosis were studied. Venous blood was examined for lymphocyte culture and chromosome aberrations. All of the ^{125}I -treated patients had lymphocytes with structural chromosome abnormalities, including ring and dicentric forms; no such abnormalities were found in lymphocytes from the 4 controls. Frequency of chromatid aberrations was similar in control and irradiated subjects. These results indicate that therapeutic doses of ^{125}I are capable of causing at least as high a level of chromosome damage in cells of the peripheral blood, and presumably also of bone marrow, as are therapeutic doses of ^{131}I . Most patients undergoing ^{125}I therapy are receiving between 10-15 mCi and have shown no hematological problems as yet. However, this study confirms that ^{131}I therapy should be reserved for adults, preferably over 40 yr of age, and that ^{125}I trials require more data concerning long-term effects.

0216 DOSE-RESPONSE RELATION OF CHROMOSOME ABERRATIONS IN HUMAN LYMPHOCYTES AFTER *IN VITRO* IRRADIATION WITH 3-MeV ELECTRONS. (E.) Schmid, E. (Inst. Biol., U. Munich, Germany), G. Rimpl and M. Bauchinger. *Radiat Res* 57(2):228-238, 1974.

Human peripheral lymphocytes were irradiated with varying doses of 3-MeV electrons, dosimetry being

carried out with Fricke solution in vessels identical to those in which the blood was irradiated. The frequency of chromosomal aberrations was then calculated and the dose-response relationship determined by fitting the data to a power law and a linear-quadratic model via least-squares regression analysis. The dicentric, dicentric + centric ring, and different acentric data gave the best fit to the linear quadratic model. The relative biological effectiveness of 3-MeV electrons versus 220 kV x-rays for dicentrics increased significantly with increasing dose in the dose range analyzed.

0217 RELATIVE EFFECTS OF WHOLE-BODY SUBLETHAL DOSES OF 60MeV PROTONS AND 300-kVp X-RAYS ON DISEASE INCIDENCES IN RF MICE. (E.) Clapp, N. K. (Oak Ridge Natl. Labs., Tenn.), E. B. Darden, Jr. and M. C. Jernigan. *Radiat Res* 57(1):158-186, 1974.

Over 3100 young adult female RF/Un mice received whole-body exposure to 60-MeV protons or 300-kVp x-rays (0-400 rads). Similar dose-response curves were seen for most of the resultant diseases and, except in cases of ovarian tumor induction, x-rays were slightly more effective in inducing a given disease than were protons. For life-shortening studies, x-rays were more effective at all doses with the greatest difference in effect occurring at the 2 lower doses, 50 and 100 rads. X-rays increased the combined incidences of thymic lymphoma and myeloid leukemia. X-rays were more effective in inducing myeloid leukemias at 50-200 rads and thymic lymphoma at 300-400 rads with no differences noted at other doses. No difference was noted in reticulum cell sarcoma and nonthymic lymphoma frequency. Lung tumors showed a negative dose-response due to failure of the animals to survive long enough to develop them. Pituitary gland and Harderian gland tumors may have been increased by radiation, but the effect was not dose dependent. Nonneoplastic diseases showed little effect from radiation. Relative biological effectiveness for 60-MeV protons was estimated at 0.63 for life-shortening and at slightly less than 1.0 for all parameters, excluding ovarian tumors.

0218 DO LASER RAYS HAVE A CARCINOGENIC ACTION? CYTOPHOTOMETRIC STUDIES ON THE DNA CONTENT OF THE EPIDERMIS AFTER EXPOSURE TO LASER RAYS. (Ger.) Ehlers, G. (Dermatology Clinic, Technical U., Munich, Germany) and H. J. Florian. *Fortschr Med* 91(19):832-834, 1973.

The effect of radiation from a ruby laser (wavelength 694.3 nm) on the epidermis and connective and fatty tissue of C57Bl mice was compared with that from a xenon strobe light. Both sources of radiation produced impulses lasting 600-800 μsec and were capable of delivering the same energy densities. Mice were exposed to 1-10 joules/cm² for 30 min/day or/wk for total doses of 10-32 joules/cm². No differences were found between the biological effects of these two types of radiation. Hair growth was first stimulated and then inhibited, and the hair lost its pigmentation after exposure to radiation.

Histological examinations showed atrophy in the first 2-3 cell layers of the irradiated epidermis in all mice given doses of more than 10 joules/cm². Degenerative changes were observed in the hair follicles and were accompanied by migration of melanin and signs of chronic inflammation in connective and fatty tissue. No signs of cell proliferation were observed. Cytophotometric determinations of the DNA content of epidermal cells revealed a significant increase in the mean DNA content and in the mean scattering of DNA values in only three of 22 mice. None of the data obtained provided either histological or cytophotometric evidence that light from the ruby laser has a carcinogenic effect.

- 0219 LOCATION AND AGE DISTRIBUTION OF SOLAR KERATOMAS. (Ger.) Hundeiker, M. (Dermatol. Clin., U. Giessen, Germany), B. Grönder and K.-G. Junge. *Arch Dermatol Forsch* 247(4):373-378, 1973.

A comparison was made of the location and age distribution of 644 solar keratomas removed from 569 patients and those of 1355 squamous cell carcinomas found in 1029 patients. The prevalence of solar keratomas increased parallel to the increase in the prevalence of squamous cell carcinoma up to the 7th decade. From the 7th decade on, the prevalence of solar keratomas decreased while that of squamous cell carcinomas increased sharply. Of the 644 solar keratomas, 352 occurred in women and 287 in men. In the younger age groups (20-40 yr), solar keratomas occurred primarily in women although the percentages of men and women are about the same in the general population in these age groups. In women the most common sites were the forehead, nose, cheeks and temples, while in men solar keratomas occurred most frequently on the head, ears and backs of the hands. On the average, women were older than men at the time of treatment. Solar keratomas were most often found on the nose in younger women and on the forehead in older women. More solar keratomas were removed from the temples in women, while most men were treated for carcinomas at this site. Solar keratomas were rarely found on the lips in either males or females, but the lips were the most common site for squamous cell carcinoma in men. Solar radiation is probably less important than exposure to tobacco tars in the development of carcinoma of the lip in men. The decreased prevalence of solar keratoma and the increased prevalence of squamous cell carcinoma in older patients may be explained by exposure to other carcinogens, the transformation of keratomas into carcinomas with a decreased prevalence of keratomas, and the tendency of older patients to neglect keratomas until they have undergone malignant transformation. Some young women had senile skin changes which resulted from year-round overexposure to the sun in an effort to keep a "healthy" tan, so the term "senile keratoma" should be replaced by "solar keratoma".

- 0220 OSTEOGENIC SARCOMA RESULTING FROM ²²⁴Ra TREATMENT. (Ger.) Spiess, H. (No affiliation) and C. W. Mays. *Helv Paediatr Acta Suppl* 132:10, 1974.

- 0221 MEASUREMENT OF DEFECTS IN ULTRAVIOLET - IRRADIATED DNA BY THE KINETIC FORMALDEHYDE METHOD. (E.) Rahn, R. O. (Oak Ridge Natl. Lab., Tenn.) and R. S. Stafford. *Nature* 248(5443):52-54, 1974.

- 0222 SKELETAL DOSE ESTIMATION OF THE PATIENT ADMINISTERED YTTERBIUM-169 CITRATE FOR TUMOR DIAGNOSIS. (E.) Anzai, I. (Fac. Med., U. Tokyo, Japan), M. Kanno, H. Tobarai and T. Higashi. *Radioisotopes* 23(1):59-63, 1974.

- 0223 RELEASE OF RIBOSOMES FROM ENDOPLASMIC RETICULUM (E.R) OF X-IRRADIATED LIVERS. (E.) Mukerjee, G. (Delafield Hosp., New York, N.Y.) and A. Goldfeder. *Radiat Res* 58(2):253-261, 1974.

- 0224 STUDIES OF LYSOSOMES AFTER IRRADIATION. II. LYSOSOMAL MEMBRANE PERMEABILITY AND ACID PHOSPHATASE ACTIVITY OF LYMPHOID AND OTHER TISSUES AFTER WHOLE-BODY IRRADIATION. (E.) Aikman, A. A. (St. Bartholomew's Hosp., London, England) and E. D. Wills. *Radiat Res* 57(3):416-430, 1974.

- 0225 STUDIES OF LYSOSOMES AFTER IRRADIATION. I. A QUANTITATIVE HISTOCHEMICAL METHOD FOR THE STUDY OF LYSOSOMAL MEMBRANE PERMEABILITY AND ACID PHOSPHATASE ACTIVITY. (E.) Aikman, A. A. (St. Bartholomew's Hosp., London, England) and E. D. Wills. *Radiat Res* 57(3):403-415, 1974.

- 0226 LETHAL EFFECT OF NEAR-ULTRAVIOLET IRRADIATION ON MAMMALIAN CELLS IN CULTURE. (E.) Wang, R. J. (Div. Biol. Sci., U. Missouri, Columbia), J. D. Stoien and F. Landa. *Nature* 247(5435):43-45, 1974.

- 0227 ULTRAVIOLET AND γ -RAY-INDUCED REACTIONS OF NUCLEIC ACID CONSTITUENTS. REACTIONS OF PURINES WITH AMINES. (E.) Salomon, J. (The Weizmann Inst. Sci., Rehovot, Israel) and D. Elad. *Photochem Photobiol* 19(1):21-27, 1974.

- 0228 PHOTOREACTIVATING ENZYME FROM HUMAN LEUKOCYTES. (E.) Sutherland, B. M. (Dept. Molec. Biol., U. Calif., Irvine). *Nature* 248(5444):109-112, 1974.

- 0229 CHROMOSOMAL ABERRATIONS OF LIVING CELLS INDUCED BY MICROWAVE RADIATION. (E.) Chen, K. M. (Dept. Elec. Eng., Michigan State U., East Lansing), A. Samuel and R. Hoopingarner. *Environ Lett* 6(1):37-46, 1974.

- 0230 INFRARED SPECTROSCOPY OF THE PHOTO- AND RADIOBIOLOGY OF DNA BASES AND THEIR DERIVATIVES. (E.) Marcus, M. A. (Rensselaer Polytech. Inst., Troy, N.Y.) and J. C. Corelli. *Radiat Res* 57(1):148-157, 1974.

0231 EFFECTS OF SINGLE-DOSE PARTIAL-BODY X-IRRADIATION ON CELL PROLIFERATION IN THE MOUSE SMALL INTESTINAL EPITHELIUM. (E.) Leshner, J. (Allegheny Gen. Hosp., Pittsburgh, Pa.) and S. Leshner. *Radiat Res* 57(1):148-157, 1974.

0232 HIGH INCIDENCE OF THYROID CARCINOMA IN UNSELECTED PATIENTS WITH A HISTORY OF IRRADIATION TO THE NECK. (E.) Refetoff, S. (Chicago, Ill.), J. Harrison, B. Karanfilski, E. L. Kaplan and L. J. DeGroot. *J Clin Invest* 53(6):64a, 1974.

0233 FIBROSARCOMA: A COMPLICATION OF INTERSTITIAL RADIATION THERAPY FOR A BENIGN HAEMANGIOMA OCCURRING AFTER 18 YEARS. (E.) Gray, G. R. (Cedars-Sinai Med. Ctr., Los Angeles, Calif.), S. I. Freedman and A. R. Kagan. *Br J Radiol* 47(553):60-61, 1974.

See also:

* (Rev): 0004, 0016, 0018, 0019, 0046
* (Chem): 0067, 0180
* (Immun): 0384

0234 DNA POLYMERASE ACTIVITIES IN VERO CELLS
INFECTED WITH HERPESVIRUS SAIMIRI. (E.)

Twardzik, D. R. (Frederick Cancer Res. Ctr., Md.), J. Simonds, G. Armstrong and D. V. Ablashi. *Bio-medicine* 21(1):1-5, 1974.

Nontrypsinized vero cells established from an African Green Monkey kidney were grown and infected on day 1 with Herpesvirus saimiri (HVS). The infected cells demonstrated increasing cytopathic effects (CPE) (70%) beginning on the sixth day post-infection; they tended to form clusters of rounded cells and differed morphologically from noninfected cells. At the time of maximum CPE, at least 80% of the cells contained nuclear virus particles. The infected cells exhibited only one of two peaks of DNA polymerase activity exhibited by non-infected cells on DEAE-cellulose and hydroxylapatite columns. The Peak I (significantly reduced in the infected cells) of the noninfected cells differed from the Peak II (exhibited by the HVS-infected cells) of these cells with respect to divalent cation requirements, heat inactivation, and inhibition of p-chloromercuribenzoate and salt. The substantial reduction in the activity of Peak I in the infected cells seems to correlate with increasing CPE, which in turn corresponds to the number of cells producing HVS.

0235 A SURVEY OF CATS AND HUMANS FOR PREVALENCE
OF FELINE LEUKEMIA-SARCOMA VIRUS NEUTRALIZING SERUM ANTIBODIES. (E.)

Sarma, P. S. (Nat'l. Cancer Inst., Bethesda, Md.), A. Sharar, V. Walters and M. Gardner. *Proc Soc Exp Biol Med* 145(2):560-564, 1974.

Sera of adult domestic cats and veterinarians and laboratory personnel involved in feline leukemia virus research were surveyed for the presence of virus neutralizing antibodies against feline leukemia-sarcoma viruses of subgroups A, B, and C. A focus neutralization test was used based on the neutralization of feline cell transforming effects of approximately 100 focus forming units of feline leukemia pseudotypes of Harvey strain of murine sarcoma virus (Harvey strain of murine sarcoma virus with the viral envelopes of the described serotypes of feline leukemia virus). Virus neutralizing envelope antibodies against one or more envelope antigenic types were found in the sera of 13 of 59 (22%) cats without neoplasia and in 9 of 38 (23.7%) cats with neoplastic disease but not in the sera of 36 veterinarians or 33 lab personnel. Thus it is suggested that cats with neoplasia as well as cats without discernible neoplastic disease are capable of responding immunologically to the viral envelope antigens of feline leukemia virus.

0236 INFECTIVITY OF BOVINE C-TYPE (LEUKEMIA)
VIRUS FOR SHEEP AND GOATS. (E.)

Hoss, H. E. (Coll. Agr. Life Sci., U. Wisconsin, Madison) and C. Olson. *Am J Vet Res* 35(5):633-637, 1974.

Of 41 lambs given infective bovine C-type virus i.p., 33 developed evidence of infection within

14 months consisting of demonstrable C-type virus, persisting or late-developing precipitins. Evidence of infection appeared earlier in the lambs when dose of the lymphocyte culture was increased. Infection was produced in lambs given cultures kept at -60 C for 10 to 14 days. Infection occurred in 6 to 8 week old lambs given lymphocyte culture i.p. Lambs receiving the culture p.o. did not have evidence of infection up to 14 months later. Buffy coat suspensions from 2 sheep with experimentally produced lymphosarcoma were infective for 7 lambs, 1 of which died with lymphosarcoma at 13 months of age. Infection was established in 3 of 4 calves and in 5 of 5 goats inoculated with bovine C-type virus from infected sheep. In testing for contact transmission, 4 lambs housed together with infected donor sheep and 20 lambs kept with inoculated lambs did not have evidence of infection after more than 12 months.

0237 PRODUCTION OF ONCORNAVIRUSES BY CELL
CULTURES. (Rus.)

Lozinskii, T. F. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), M. Ia. Volkova, U. A. Abenova, N. N. Mazurenko, G. G. Miller, I. A. Irlin, K. V. Il'in, A. F. Bykovskii, B. V. Gushchin, S. M. Klimenko and V. M. Zhdanov. *Vopr Onkol* 20(1):56-62, 1974.

Investigations were made of type B oncornavirus production by HEp-2, HeLa, A1, RH, DAPT, and Detroit-6 cell cultures after labeling with ³H-uridine. Gradient density centrifugation in a sucrose gradient showed that type B virions were present in the 1.16-1.17 g/ml fraction, while paramyxoviruses occurred in the 1.18-1.19 g/ml fraction and *Mycoplasma* in the 1.21-1.23 g/ml fraction. Reverse transcriptase activity was present when type B virions were present in culture fluid but was not detected when cultures began to produce paramyxovirus and *Mycoplasma*. Although oncornavirus particles and reverse transcriptase activity were found inside the cells at all times, they were not always present in the culture medium. These findings suggest that paramyxoviruses and *Mycoplasma* may interfere with the final phase of oncornavirus replication in which the external membrane is formed and the virus emerges from the cell. Preliminary experiments indicate that removal of contaminants from the culture is accompanied by an increase in oncornavirus appearing in the culture fluid.

0238 ONCORNA VIRUS DISEASE. THE SYNDROME OF
HEMOLYTIC ANEMIA AND LYMPH NODE CYSTIC

DISEASE. (E.) Siegler, R. (Children's Cancer Res. Fdn., Boston, Mass.), S. Moran, B. Glader, I. Lane and Y. Frosch. *Lab Invest* 30(5):626-638, 1974.

Newborn CD rats inoculated with virus stocks containing rat anemia virus developed a profound hemolytic anemia within 2 weeks. Marked erythroblastosis occurred in the spleen, restoring the erythrocyte count to normal by the 45th day in surviving rats. This splenic erythroblastosis has

histologic resemblance to Friend-Rauscher disease. It has been suggested that a direct viral absorption onto, and alteration of, the red cell membrane, resulting in sequestration and destruction of such cells by the spleen is the mechanism by which this virus-induced hemolytic anemia functions. Massive cystic changes of lymph nodes occurred in virus-inoculated rats and were usually fatal. This lesion began with progressive distention of the efferent lymphatic vessels of the peripheral lymph nodes, which eventually replaced the node with a large lymph-filled cyst. The lymph node cysts may arise due to massively increased plasma filtration across the medullary cords. The plasma filtration through the fine mesh of the lymph node cells was associated with active phagocytosis of virus by endothelial cells of the postcapillary venules, and by macrophages within the medullary cords. This passage of plasma through the node is a normal functional mechanism by which virus is cleared from the blood. Therefore, disease and death from the oncornavirus result from highly exaggerated, progressively activated natural physiologic mechanisms, activated by unique host-virus interaction.

- 0239 REPLICATION OF THE RESIDENT REPRESSED EPSTEIN-BARR VIRUS GENOME DURING THE EARLY S PHASE (S-1 PERIOD) OF NONPRODUCER RAJI CELLS. (E.) Hampar, B. (Nat'l. Cancer Inst., Bethesda, Md.), A. Tanaka, M. Nonoyama and J. G. Derge. *Proc Nat Acad Sci USA* 71(3):631-633, 1974.

Nonproducer Raji cells were synchronized and at intervals samples were harvested for extraction of DNA and hybridization with EB virus-specific cRNA. Approximately 85% cell synchrony was obtained. Results indicate that replication of the EB virus genome occurred during the interval between 30-90 min of the first S phase following reversal of the dT block. The time of replication of the resident EB virus during the second S phase following reversal of the dT block was investigated. The degree of synchrony during the second S phase was not as high as during the first. Results localized the time of replication to the S-1 period of the second S phase following reversal of the dT block. The S-1 period was previously identified as the critical period for virus activation induced by thymidine analogues. The findings of this study and others suggest that virus activation is initiated at or near the site of association of the resident viral genome with cell DNA, that replication of the resident virus genome in nonactivated cells is under cell control mechanisms, and that the resident virus genome is physically associated with early replication cell DNA.

- 0240 EXTENT OF TRANSCRIPTION OF MOUSE SARCOMA-LEUKEMIA VIRUS BY RNA-DIRECTED DNA POLYMERASE. (E.) Tavittian, A. (Hosp. St. Louis, Paris, France), R. Hamelin, P. Tchen, B. Olofsson and M. Boiron. *Proc Natl Acad Sci USA* 71(3):755-759, 1974.

The DNA product obtained from the endogenous RNA-directed DNA polymerase (deoxynucleosidetriphos-

phate:DNA deoxynucleotidyltransferase) reaction of the Moloney sarcoma:leukemia viruses produced by the 78 A-1 cell line was analyzed and characterized. The extent of transcription of viral 70S RNA was measured by RNA-DNA hybridization (^{32}P -viral RNA- ^3H product DNA). No double-stranded DNA was obtained. The product consisted of 95-99% single-stranded DNA with an average length of 200 nucleotides. In contrast to the results reported with avian and other RNA oncogenic viruses, it was found that the entire 70S viral RNA genome was transcribed into DNA pieces and that a small excess of the product DNA was sufficient to anneal the 70S RNA and render it totally resistant to single-stranded-specific enzyme digestion.

- 0241 METABOLIC DIFFERENCES BETWEEN NORMAL AND NEOPLASTIC CELLS: EFFECTS OF AMINONUCLEOSIDE ON CYTOPLASMIC MESSENGER RNA. (E.) Cholon, J. J. (Med. Coll. Jefferson U., Philadelphia, Pa.) and G. P. Studzinski. *Science* 184(9133):160-161, 1974.

The question of whether the appearance of messenger RNA (mRNA) in the cytoplasm is inhibited by aminonucleoside in normal human fibroblasts, but not in SV40-transformed fibroblasts has been considered. Poly(a)-containing RNA from control cultures shows the distribution expected of cytoplasmic mRNA, but the appearance of RNA of this type in the cytoplasm is virtually suppressed by exposure to cordycepin (3'-deoxyadenosine) for 60 minutes in both normal human fibroblasts and in SV40-transformed fibroblasts. The effect of aminonucleoside, however, is clearly selective. Little mRNA could be detected in the cytoplasm of normal cells treated with aminonucleoside, while the amount of cytoplasmic mRNA is unaffected by this treatment of transformed cells.

- 0242 FELINE "FOAMY" VIRUSES: INCIDENCE IN AUSTRALIA. BRIEF REPORT. (E.) Sabine, M. (Dept. Vet. Path., U. Sydney, Australia) and D. N. Love. *Arch Gesamte Virusforsch* 43(4):397-400, 1973.

In contrast to the experience in California and other parts of the United States and Great Britain, adult feline cells in Australia propagate well *in vitro*. Cultures of cat kidney cells have frequently been kept in culture for 21 days or longer, the maximum time tested being 71 days. Although feline foamy viruses and C-type viruses share many biological properties, the two groups differ in their morphogenesis, as revealed by electron microscopic examination. Tissues from 11 cats with spontaneous lymphosarcoma were examined and nine contained budding and extracellular C-type particles, but no foamy viruses. Neither were foamy viruses seen in 25 primary adult cat kidney cultures infected with calicivirus. No feline foamy viruses have been isolated in Australia or New Zealand, indicating that, perhaps because of strict quarantine laws, Australian cats are relatively, if not completely, free from feline foamy viruses.

- 0243 DETECTION OF ANTIGENS DETERMINED BY THE EPSTEIN BARR VIRUS (EBV) IN HUMAN LYMPHOBLASTOID CELL CULTURE LINES BY ELUTION OF SPECIFIC RADIOIODINE LABELED ANTIBODY. (E.) Lamon, E. W. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), I. Ernberg and G. Klein. *Clin Immunol Immunopathol* 2(2):216-233, 1974.

Antigens determined by Epstein-Barr virus (EBV) in lymphoblastoid cell lines derived from Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC) biopsies were defined and quantitated by elution of specific radioiodine labeled antibodies (RIE) from live target cells. Early antigen (EA), but not viral capsid antigen (VCA), appeared in antigen negative cell lines treated with 5-iododeoxyuridine (IUDR) or superinfected with EBV in the presence of cytosine arabinoside (Ara C). When these preparations were exposed to labeled human EA and VCA reactive antibody and the bound fraction eluted at pH 2.8, there was a good correlation between the peak of elutable radioactivity and the percentage of EA positive cells by immunofluorescence. Labeled Ig with EA and VCA specificity competed with unlabeled membrane antigen (MA) and VCA positive (EA negative) serum for reactive sites on target cells expressing all three antigens. Successful antibody competition indicated that the reactants were competing for VCA. EBV superinfection in the presence of Ara C induced EA and MA but no VCA in an originally antigen negative cell line. The binding and subsequent elution of a labeled MA+, EA-, VCA+ Ig from these cells demonstrated anti-MA activity which was lessened after each wash. The specificity of the antibody binding and elution was demonstrated by successful antibody competition with sera containing corresponding antibodies, but not with EBV negative human serum (NHS). Labeled Ig from NHS did not bind to the positive target cells in a paired radioiodine labeled antibody test. Labeled EBV-reactive Ig bound selectively to the antigen positive "producer" lines but not to antigen negative "nonproducer" lines. Antigen induction by graded doses of superinfecting EBV was quantitated by the RIE technique in one of the originally antigen negative cell lines. There was good agreement between the level of antigen induction as judged by immunofluorescence and the amount of eluted radiolabeled Ig.

- 0244 dsDNA MADE BY RNASE-SENSITIVE DNA POLYMERASE FROM RSV-TRANSFORMED CELLS. (E.) Kotler, M. (Lab. Molecular Virol., Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel), O. Haspel and Y. Becker. *Nature* 249(5456):441-445, 1974.

The nature of the template and the role of RNA in the synthesis of DNA by the cytoplasmic RNase-sensitive DNA polymerase activity found in rat embryo fibroblasts transformed by the B77 strain of Rous sarcoma virus (R(B77) cells) were studied. The results confirmed the presence of an RNase-sensitive DNA polymerase activity in the R(B77) cells, and demonstrated that the high speed pellet (HSP) preparations from the R(B77) cells contain 10S DNA molecules of cellular origin which act as

the template for this enzymatic activity. RNA also has a function in the synthesis of DNA since nascent DNA molecules, covalently linked to RNA, were synthesized at the very beginning of the reaction. Thus, the HSP DNA polymerase activity is an RNA-dependent DNA polymerase which utilizes the cellular double-stranded DNA molecules present in HSP as template.

- 0245 COMMON ANTIGENS IN HERPESVIRUSES FROM DIVERGENT SPECIES OF ANIMALS. (E.) Evans, D. L. (U. Texas System Cancer Ctr., Houston), J. W. Barnett and L. Dmochowski. *Tex Rep Biol Med* 31(4):755-770, 1973.

Using complex heterologous antisera prepared against infectious bovine rhinotracheitis (IBR) and Epstein-Barr (EBV - Burkitt's lymphoma) viruses, 10 different herpesviruses from mammalian, avian, and amphibian species were found to have several common antigens. Immunodiffusion tests with these antisera revealed a common antigen in herpesvirus saimiri, IBR, EBV, herpes simplex type I, pseudorabies virus, and infectious bovine keratoconjunctivitis (IBKC). Immunoelectrophoresis with both antisera revealed at least three antigens common to EBV, IBR, IBKC, and infectious mononucleosis. Two of the three antigens were observed (using either IBR or EBV antiserum) in pseudorabies and herpes simplex type I, and one was found in Marek's disease and bovine ocular squamous cell carcinoma preparations. Counterelectrophoresis studies of the herpesvirus of Lucké renal adenocarcinoma of the frog revealed one common antigen with IBR and EBV. In addition, using immunodiffusion tests, one type-related antigen was observed in both IBR and EBV antigen preparations in the presence of each respective homologous antiserum.

- 0246 VIRAL DNA-RNA HYBRIDS IN CELLS INFECTED WITH SIMIAN VIRUS: THE SIMIAN VIRUS 40 TRANSCRIPTIONAL INTERMEDIATES. (E.) Girard, M. (Inst. Sci. Res. Cancer, Villejuif, France), L. Marty and S. Manteuil. *Proc Natl Acad Sci USA* 71(4):1267-1271, 1974.

CV1 cells were infected with the large plaque type of simian virus 40 (SV40), labeled with uridine, treated with cytosine arabinoside (ara-C), and the labeled material extracted and processed. Part of the label was incorporated into material which was soluble in 1 M NaCl and sensitive to KOH, with a buoyant density close to that of DNA. This material was shown to consist of DNA-RNA hybrid molecules which were absent from uninfected cells. In addition, their RNA portion specifically hybridized with SV40 DNA, the kinetics of their labeling with a radioactive precursor to RNA were not linear with time, the labeled material recovered the density of RNA after melting or treatment with DNase, the rate of SV40 mRNA synthesis varied in close parallel to the accumulation of hybrid molecules, and the RNA was heterogeneous in size, but smaller than mature viral mRNA. The RNA from the hybrid differed from an RNA primer, indicating that the DNA-RNA hybrids represent active

SV40 transcriptional complexes made of nascent viral mRNA molecules attached through hydrogen-bonding to their DNA templates. The DNA in the hybrids seems to be in the form of replicative intermediate molecules. It is suggested that the DNA-RNA complexes be termed viral transcriptional intermediates (TI).

- 0247 INDUCTION OF δ -AMINOLEVULINIC ACID SYNTHETASE DURING ERYTHROID DIFFERENTIATION OF CULTURED LEUKEMIA CELLS. (E.) Ebert, P. S. (Natl. Cancer Inst., Bethesda, Md.) and Y. Ikawa. *Proc Soc Exp Biol Med* 146(2):601-604, 1974.

The induction of δ -aminolevulinic acid (ALA) synthetase, an inducible mitochondrial enzyme which is the control enzyme for the heme pathway, was studied in dimethyl sulfoxide (DMSO)-treated T-3-C1-2 cells, a cloned line of murine proerythroblastoid cells transformed by Friend leukemia virus. The addition of DMSO (1-2%) induced the synthesis of hemoglobin by these cells within 7 days. In comparison with partially purified rat liver succinic thiokinase and succinate-2,3- 14 C, 2-ketoglutarate-5- 14 C was the most efficient substrate for 14 C-ALA production in this cell line. DMSO in concentrations of 1-3% elevated the activity of ALA synthetase, with 2% DMSO producing the optimal induction of enzyme activity. The time course of induction and repression of the enzyme varied with the concentration of DMSO. Allyliso-propylacetamide, a potent inducer of ALA synthetase in rats, was as effective an inducer of ALA synthetase as 1% DMSO, and could augment the enzyme activity when present with DMSO.

- 0248 DIFFERENCES IN THE SURFACE MOBILITY BETWEEN NORMAL AND SV40-, POLYOMA- AND ADENOVIRUS-TRANSFORMED HAMSTER CELLS. (E.) Huet, Ch. (Inst. Res. Cancer, Villejuif, France) and W. Bernhard. *Int J Cancer* 13(2):227-239, 1974.

Living cultures of normal hamster fibroblasts and hamster cells transformed by simian virus 40 (SV40) polyoma, adenovirus 12, and simian adenovirus 7 were labeled *in situ* by 63 Ni-Concanavalin A (Con A) as well as by Con A plus wheat germ agglutinin (WGA), as revealed cytochemically using horseradish peroxidase (PO) and negative colloidal iron. The cells were then incubated at 37 C in PBS for 8 minutes to 4 hours, after which they were examined by electron microscopy. Con A labeling revealed differences in the surface between the normal and virus-transformed cells: the transformed cell lines showed a much greater membrane mobility in that most of the Con A/PO labeled material disappeared from the cell surface 15 to 45 minutes earlier than from the surfaces of the normal cells. Measurements of radioactive Con A showed that most of the lectin penetrated into the cell, and that shedding of the labeled cell coat material into the medium was minimal. With the negative colloidal iron, the available amino groups were labeled and the same difference in surface movements was again observed. The WGA/PO complex revealed no differences between the normal

and transformed cells. Rapid penetration occurred with all cells, but some label always remained at the surface.

- 0249 CHARACTERISTICS OF MURINE C-TYPE VIRUSES. IV. THE VIRUS PRODUCED BY EHRLICH TUMOR CELLS AND ITS HYBRIDS WITH MOUSE L CELLS. (E.) Grundner, G. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), E. M. Fenyö and E. Klein. *Int J Cancer* 13(3):420-427, 1974.

The infectious properties of viruses produced by Ehrlich tumor cells (E), the A9 subline of mouse L cells (L), their hybrids (EL₀ and EL), and highly malignant sublines of the low-malignant hybrid line (EL_m) were investigated. The infectivity assays included antigen induction on JLS-V9 cells, antigenic conversion and focus induction on S+L-cells (D56 subline), and focus formation on BALB/3T3 cells. The E and L viruses, produced by the parental cells, were detected in the JLS-V9 test but were distinguished in the S+L- and BALB/3T3 cells. The L virus was focus-positive and the E virus was focus negative (BALB/3T3), while, for antigenic conversion, the L virus was negative and the E virus was positive (D56). The hybrid cell line, tested on several occasions after the hybridization event, produced viruses with characteristics similar to both the E and L virus, regardless of the complete or reduced chromosome numbers. The malignant sublines selected from the hybrid showed preferential loss of the A9 parent-derived biallelic chromosomes. One of these lines produced virus (EL_m) with infective properties similar to those of the E virus. This suggests that the virus produced by a particular cell line is determined by the cell genome. Another malignant cell subline was negative for the production of infectious virus in all three indicator systems.

- 0250 MURINE VIRUS-INDUCED PROTEINS SYNTHESIZED BY HAMSTER TUMOR CELLS TRANSFORMED BY, BUT NOT PRODUCING, MURINE SARCOMA VIRUS. (E.) Ikegami, N. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.) and P. J. Gomatos. *J Virol* 13(2):500-512, 1974.

A transformed cell line (8303) derived from a hamster tumor induced by the Moloney strain of murine sarcoma virus (M-MSV) contains murine virus-induced proteins but does not produce virus particles. The virus-induced proteins within the cells were identified as free proteins or as existing in association with membranous material, including the plasma membrane. In addition, some of the proteins were excreted by the cells into the growth medium. Most of the virus-induced proteins were larger than 68,000 daltons and they did not dissociate into components of small size in the presence of detergent and a reducing agent. A small amount of virus-induced protein with a molecular weight of less than 20,000 was also found in the 8303 cells. No virus-specific proteins with the identical antigenic specificity or size of the major internal group specific antigen (molecular weight about 30,000) of the murine leukemia viruses

were present. The reactivity of the murine virus-induced antigen of the 8303 hamster tumor cells is identical to that of the cell surface antigen found in four other virus-producing and non-virus-producing tumor cell lines (RRTC rat tumor cells, XC rat tumor cells, L929 mouse fibroblasts, and JLS-V9 cells). This antigen is not present on the cell surface of normal mouse embryo cells. The presence of this common cell surface antigen on these five cell lines suggests that the cell surface of each contains a common protein of interspecies viral specificity; this protein may be a tumor-specific antigen concerned with the maintenance of the transformed state or tumorigenic capacity.

0251 COMPARISON OF EBV NEUTRALIZATION TESTS BASED ON ABORTIVE INFECTION OR TRANSFORMATION OF LYMPHOID CELLS AND THEIR RELATION TO MEMBRANE REACTIVE ANTIBODIES (ANTI-MA). (E.)

De Schryver, A. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), G. Klein, J. Hewetson, G. Rocchi, W. Henle, G. Henle, D. J. Moss and J. H. Pope. *Int J Cancer* 13(3):353-362, 1974.

Epstein-Barr virus (EBV)-neutralizing (N) antibodies were assayed in 62 human sera (24 from Burkitt's lymphoma (BL) patients, 20 from nasopharyngeal carcinoma (NPC) patients, seven from infectious mononucleosis (IM) patients, and 11 from donors without malignant disease) using techniques based on: early antigen (EA) synthesis in lymphoblasts (NEA); inhibition of colony formation by lymphoblasts (NICF); and cord-blood lymphocyte transformation (NLT). A good correlation was noted between the NEA and NICF titers of 41 sera so tested. The correlation among NEA and NICF and NLT titers was less pronounced, possibly because only 22 sera were tested by the latter method. Limited to concordant sera, i.e., sera with high or low titers for both antibodies to EB viral capsid antigens (VCA) and to EBV-determined cell membrane antigens (MA), the N titers determined by the three methods showed a good correlation with the anti-MA titers, as did the few discordant sera with high anti-MA but low anti-VCA titers. However, some discordant sera with low anti-MA and high anti-VCA titers also showed substantial N titers. The mean anti-VCA titers were equal in the concordant and discordant groups (553); the anti-MA (BT) titers were 25 and ≤ 1.4 , respectively; and the neutralization titers were 209 (NEA), 204 (NICF), and 523 (NLT) in the concordant group, as compared with 128, 74, and 99, respectively, in the discordant group. These data support the contention that lymphoblast transformation and EA induction and inhibition of lymphoblast colony formation are induced by the same type of viral particle.

0252 DETECTION OF A PROTEIN OF AVIAN LEUKOVIRUSES IN UNINFECTED CHICK CELLS BY RADIOIMMUNOASSAY. (E.) Chen, J. H. (Rockefeller U., New York, N.Y.) and H. Hanafusa. *J Virol* 13(2):340-346, 1974.

The quantity of the P27 protein (mol wt 27,000;

group specific-1 (gs-1)) of avian leukoviruses (Rous-associated virus 2 (RAV-2)), the Bryan strain of Rous sarcoma virus (B-RSV), and the B77 strain of avian sarcoma virus) was measured in various adult and embryonic chicken cells using monospecific anti-P27 serum and radioimmunoassay (RIA) techniques. The RIA used was 200- to 300-fold more sensitive than the complement fixation test and was able to detect as little as 0.3 ng of P27. Among six embryos which were negative for gs antigen (tested by complement fixation) and helper activity, P27 was undetectable in three embryos, while the other three contained about 5 ng of P27 per mg of cell protein by RIA. The amount of P27 in the gs antigen-positive cells ranged from 22 to 57 ng per mg of cell protein. P27 was found in the liver, lung, ovary, feather pulp, and spleen from adult gs antigen-positive chickens. This protein was not detectable in the various tissues from gs antigen-negative adult chickens.

0253 ISOLATION AND CHARACTERIZATION OF A PAPOVAVIRUS FROM HUMAN URINE. (E.) Dougherty, R. M. (Dept. Microbiol., St. U. New York, Upstate Med. Ctr., Syracuse) and H. S. DiStefano. *Proc Soc Exp Biol Med* 146(2):481-487, 1974.

A virus (RFV) isolated from the urine of a human renal transplant patient and grown in human embryo kidney (HEK) cell culture had properties associated with the polyoma-simian virus 40 (SV40) subgroup of papovaviruses. Virions with papovavirus capsomeric structure, 37-43 nm in diameter, contained circular, supercoiled DNA of 2.9×10^6 daltons. Density gradient analysis revealed two classes of particles in infected cell cultures: full virions at 1.34 g/cm^3 and empty virions at 1.29 g/cm^3 . Both the full and empty particles agglutinated human O erythrocytes. Both infectivity and hemagglutination were resistant to chloroform. Hemagglutination-inhibition (HI) tests and plaque neutralization tests in HEK cells indicated that RFV was related, but distinct from SV40. Antibodies against RFV were present in at least 81% of 400 adult human sera and high titers of HI antibodies against RFV were present in pooled human immune globulin. Of the known human papovaviruses, RFV most closely resembles the BK strain.

0254 CONTROL OF SIMIAN VIRUS 40 GENE EXPRESSION IN ADENOVIRUS-SIMIAN VIRUS 40 HYBRID VIRUSES: SYNTHESIS OF HYBRID ADENOVIRUS 2-SIMIAN VIRUS 40 RNA MOLECULES IN CELLS INFECTED WITH A NONDEFECTIVE ADENOVIRUS 2-SIMIAN VIRUS 40 HYBRID VIRUS. (E.) Oxman, M. N. (Virus Res. Unit, Children's Hosp. Med. Ctr., Boston, Mass.), M. J. Levin and A. M. Lewis, Jr. *J Virol* 13(2):322-330, 1974.

The effect of interferon on simian virus 40 (SV40) and adenovirus 2 (Ad2) T antigen synthesis was examined in African green monkey kidney cells infected with SV40, Ad2, or a nondefective Ad2-SV40 hybrid virus (Ad2+ND₄). The induction of SV40 T antigen by SV40 was highly sensitive to interferon, whereas the induction of Ad2 T antigen by Ad2 was resistant. This difference in interferon

sensitivity was also noted in cells simultaneously infected with both viruses. However, the induction of SV40 T antigen by Ad2+ND₄, which contains covalently linked SV40 and Ad2 DNAs, was as resistant to interferon as was the induction of Ad2 T antigen. This change in the interferon sensitivity of SV40 T antigen synthesis suggests that the expression of at least this portion of the SV40 genetic information in Ad2+ND₄ is under Ad2 genetic control. When RNA extracted from Ad2+ND₄-infected cells was examined by means of sequential hybridization with Ad2 DNA, elution, and rehybridization with SV40 DNA, 27% was detected in control mixtures of Ad2 and SV40 RNAs. The presence of Ad2 and SV40 nucleotide sequences in the same RNA molecule indicates that, in Ad2+ND₄ infection, transcription is initiated in the DNA of one virus (Ad2 or SV40) and continues without interruption across the point of junction into the DNA of the other virus. Furthermore, the interferon resistance of Ad2+ND₄-induced SV40 T antigen synthesis suggests that transcription of the genetic information for SV40 T antigen is initiated in a region of Ad2 DNA.

0255 INTRACELLULAR VIRUS-SPECIFIC STRUCTURES AND RNAs IN ONCORNAVIRUS-PRODUCING HUMAN CELLS. (E.) Bukrinskaya, A. G. (Acad. Med. Sci., Moscow, USSR), G. G. Miller, E. N. Lebedeva and V. M. Zhdanov. *J Virol* 13(2):478-487, 1974.

Two kinds of virus-specific structures were isolated from the cytoplasm of Detroit-6 and human amnion cells producing oncornavirus-like particles. These structures represented A particles with diameters of 70 to 80 nm and aggregated strands of nucleocapsids with diameters of 3 to 6 nm. The structures were separated from cellular contaminants by isopycnic banding in linear sucrose gradients and subsequently further purified by sedimentation in velocity sucrose gradients. Their sedimentation coefficients were 250 and 150S, respectively. Both structures contained 60, 45, and 35S RNA species, and the 150S structures also contained 20S RNA. The 35 and 20S RNA from the 150S structures formed hybrids with the DNA enzymatically synthesized on extracellular virions. The structures displayed endogenous polymerase activity, the DNA product of the reaction being predominantly associated with the 60S RNA. No 70S RNA was found in the cell structures of various densities, although the virions purified from the tissue culture fluid contained 70S RNA. These data are consistent with those indicating an extracellular maturation of virion RNA among C type oncornaviruses.

0256 STRUCTURAL STUDIES OF AVIAN MYELOBLASTOSIS VIRUS: COMPARISON OF POLYPEPTIDES IN VIRION AND CORE COMPONENT BY DODECYL SULFATE-POLYACRYLAMIDE GEL ELECTROPHORESIS. (E.) Stromberg, K. (Nat'l. Cancer Inst., Bethesda, Md.), N. E. Hurley, N. L. Davis, R. R. Rueckert and E. Fleissner. *J Virol* 13(2):513-528, 1974.

Two different systems of dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) in separate laboratories revealed analogous dye band patterns

in virions of avian myeloblastosis virus (AMV). At least 11 of the dye bands co-migrated with the major polypeptides reported for the Rous sarcoma virus. Particles with the morphology of the AMV core component, obtained after exposure of AMV to the nonionic surfactant Sterox SL, contained the major polypeptides p12, p27, p60, p64, p91, and p98. The polypeptide p12 was previously shown to be the major constituent of the inner ribonucleoprotein (RNP) of the AMV core and has been designated p12(N). Two RNP polypeptides, p64 and p91, co-electrophoresed with purified AMV DNA polymerase and have been designated p64(p) and p91(P). The polypeptide p27 is a probable constituent of the core shell and has been designated p27(C). In comparison to AMV virions, the AMV core component contained a greatly reduced amount of polypeptide p15 and appeared to lack the major polypeptide p19. Consequently, these polypeptides may be associated either with the exterior of the core shell or the interior of the viral envelope. Glycopeptides were not detected in the AMV cores, in agreement with earlier reports that they reside in external projections from the viral envelope.

0257 STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: POLYPEPTIDES AND GLYCOPROTEINS. (E.) Teramoto, Y. A. (Sch. Med., U. California, Davis), M. J. Puentes, L. J. T. Young and R. D. Cardiff. *J Virol* 13(2):411-418, 1974.

The polypeptide and glycoprotein composition of mouse mammary tumor virus (MTV) virions obtained from primary monolayer cultures of BALB/cfC3H mouse mammary tumor cells was studied by polyacrylamide gel electrophoresis using internal and external labeling and Coomassie blue and periodic acid Schiff (PAS) staining. Twelve polypeptides were reproducibly resolved using the combined methods. Five major polypeptides with estimated molecular weights of 52,000, 36,000, 28,000, 14,000, and 10,000 daltons were demonstrated. Seven minor polypeptides with estimated molecular weights of 70,000, 60,000, 46,000, 38,000, 30,000, 22,000, and 17,000 daltons were also consistently detected. Carbohydrate was associated with five of these polypeptides as measured by PAS staining and/or (³H)glucosamine labeling; these glycoproteins had estimated molecular weights of 70,000, 60,000, 52,000, 36,000, and 10,000 daltons. The majority of the PAS stain and glucosamine was incorporated into the 52,000 and 36,000 dalton peaks.

0258 RELATIONSHIP OF mRNA FROM PRODUCTIVELY INFECTED CELLS TO THE COMPLEMENTARY STRANDS OF ADENOVIRUS TYPE 2 DNA. (E.) Tibbetts, C. (Dept. Microbiol., Wallenberg Lab., Uppsala U., Sweden), U. Pettersson, K. Johansson and L. Philipson. *J Virol* 13(2):370-377, 1974.

The complementary strands of adenovirus type 2 (Ad2) DNA were separated by buoyant density gradient centrifugation with poly (U,G). The complementary strand DNA remained intact through the course of strand separation. The 1-strand of Ad2 DNA,

appearing in the less dense complex with poly(U,G) in neutral CsCl density gradients, had a bouyant density in alkaline (pH 12.5) CsCl gradients which was 2 to 3 mg/ml greater than that of its complement (h-strand). Renaturation of the purified complementary strand DNA was observed only in mixtures of h- and l-strand DNA, and then with the second-order reaction rate expected for Ad2 DNA. Hybridization of the complementary strands with cytoplasmic mRNA isolated from infected HeLa cells was performed in liquid phase and analyzed by hydroxylapatite chromatography. Prior to viral DNA synthesis (6 hours after infection), 13 to 18% of the h-strand and 30 to 35% of the l-strand were represented in the viral mRNA. Eighteen hours after infection, the mRNA represented 20 to 25% and 63 to 68% of the h- and l-strands, respectively. Thus, most, if not all, of the sequences present in the viral mRNA prior to DNA synthesis were also present in the cytoplasm late in infection.

0259 INTERACTIONS OF POLYOMA AND MOUSE DNAs.
II. POLYOMA-INDUCED MOUSE DNA REPLICATION AND PSEUDOVIRION FORMATION. (E.) Türlér, H. (Dept. Molecular Biol., U. Geneva, Switzerland). *J Virol* 13(2):285-290, 1974.

Secondary mouse embryo (ME) cultures grown in the presence of 5-bromodeoxyuridine (BUdR) and 5-fluorodeoxyuridine have been found to be permissive for polyoma virus infection. The DNA extracted from the progeny virus yielded two bands on CsCl₂ isopycnic centrifugation. The light band (LL) contained supercoiled circular (polyoma DNA I), open circular (polyoma DNA II), and linear (polyoma DNA III) molecules, as revealed by electron microscopy. The hybrid band (HL), in which bromouracil (BU) substituted for thymine in one strand, contained exclusively linear molecules. This DNA was pure, density-labeled, pseudovirion DNA, i.e., fragmented HL mouse DNA. Quantitative comparison of the HL and LL polyoma DNA III from six different virus preparations always revealed an excess of HL DNA, the ratio of HL:LL being between 1.2 and 2.2. These data indicate that in BUdR-prelabeled, polyoma-infected ME cells, pseudovirion DNA is excised from both unreplicated and newly replicated regions of mouse DNA.

0260 ACQUISITION OF NEW DNA SEQUENCES AFTER INFECTION OF CHICKEN CELLS WITH AVIAN MYELOBLASTOSIS VIRUS. (E.) Shoyab, M. (U. California, Sch. Med., Los Angeles), M. A. Baluda and R. Evans. *J Virol* 13(2):331-339, 1974.

DNA-RNA hybridization studies using 70S RNA from avian myeloblastosis virus (AMV) and an excess of DNA from AMV-induced leukemic chicken myeloblasts or a mixture of normal and congenitally infected K-137 chicken embryos producing avian leukosis viruses revealed the presence of fast- and slow-hybridizing virus-specific DNA sequences. However, the leukemic cells contained twice the level of AMV-specific DNA sequences observed in normal chicken embryonic cells. The fast-reacting

sequences were 2 to 3 times more numerous in the leukemic DNA than in the DNA from the mixed embryos. The slow-reacting sequences had a reiteration frequency of approximately 9 and 6 in the two respective systems. Both the fast- and slow-reacting DNA sequences in the leukemic cells exhibited a higher dissociation temperature (T_m) (2 C) than the respective DNA sequences in the normal cells. In both the normal and leukemic cells, the slow hybrid sequences appeared to have a T_m which was 2 C higher than that of the fast hybrid sequences. Individual non-virus-producing chick embryos, either group-specific antigen positive or negative, contained 40 to 100 copies of the fast sequences and 2 to 6 copies of the slowly hybridizing sequences per cell genome. Normal rat cells did not contain DNA which hybridized with AMV RNA, whereas non-virus-producing rat cells transformed by B-77 avian sarcoma virus contained only the slowly reacting sequences. These results indicate that leukemic cells transformed by AMV contain new AMV-specific DNA sequences which are not present before infection.

0261 EPSTEIN-BARR VIRUS: TRANSFORMATION OF NON-HUMAN PRIMATE LYMPHOCYTES *IN VITRO*. (E.) Falk, L. (Dept. Microbiol., Rush-Presbyterian-St. Luke's Med. Ctr., Chicago, Ill.), L. Wolfe, F. Deinhardt, J. Paciga, L. Dombos, G. Klein, W. Henle and G. Henle. *Int J Cancer* 13(3):363-376, 1974.

Continuous lymphoblastoid cell cultures were established from marmoset (*Sanguinus* sp.), squirrel (*Saimiri sciureus*), owl (*Aotus trivirgatus*), and cebus (*Cebus apella*) monkeys after culturing their peripheral lymphocytes with lethally X-irradiated cells carrying Epstein-Barr virus (EBV). Transformation was also achieved by exposing simian lymphocytes to infectious, cell-free EBV derived from HR-1 cells. The simian cell cultures were similar to cell cultures derived from Burkitt's lymphoma or infectious mononucleosis patients. EBV-induced early, viral capsid, and membrane antigen, intranuclear inclusion bodies, and herpesvirus virions were demonstrable in most cultures. Seven cultures were not susceptible to superinfection with EBV and treatment of these cultures with halogenated pyrimidines was relatively ineffective in inducing the synthesis of early or viral capsid antigens. All cell cultures had B-cell characteristics; they produced immunoglobulins but did not form spontaneous rosettes with sheep erythrocytes. Four of the six marmoset monkeys inoculated with EBV-transformed marmoset lymphocytes, developed antibodies to EB viral capsid antigens, and one marmoset inoculated with autochthonous transformed cells also developed heterophile antibodies. Seven marmosets, inoculated with cell-free EBV derived from HR-1 cell cultures, developed no detectable levels of antibodies to EBV-specified antigens or heterophile antibodies. No overt clinical abnormalities were detected in any of the marmosets inoculated with HR-1 or Kaplan EBV, but one of the five marmosets inoculated with B95-8 EBV developed a lymphoma.

- 0262 COMPARATIVE DIFFERENTIATION AND NUMERATION OF CFUs FROM MICE INFECTED EITHER BY THE ANEMIA- OR POLYCYTHEMIA-INDUCING STRAINS OF FRIEND VIRUSES. (E.) Wendling, F. (Inst. Radium--Fdn. Curie, Orsay, France), P. Tambourin, O. Gallien-Lartigue and M. Charon. *Int J Cancer* 13(4): 454-462, 1974.

A comparative study of alterations in the CFU (colony-forming unit) compartment of susceptible Swiss mice infected with the anemia- (FVA) or the polycythemia-inducing strain of Friend virus (FVP) indicated that: whatever the type of virus used, the absolute number of CFU is increased in the spleen and blood; the splenic CFU augmentation parallels the increase in cellularity so that the CFU concentration remains equal to that of control spleens; circulation of the CFU in the peripheral blood is multiplied by a factor of about 100 in FVA-infected mice and 500 in FVP-infected mice 25 days after infection; and in the femoral bone marrow, the CFU number is either unaltered (FVP infection) or decreased (FVA infection). Stem cells from leukemic mice are able to give rise to colonies of differentiated hematopoietic cells, as are control CFU. The distribution of the various types of colonies is similar between the different tissues and the different groups of donors. Despite considerable differences between FVA and FVP pathological erythropoiesis, no qualitative discrepancies are observed between the population sizes and the differentiating abilities of the pluripotential stem-cell compartment. The increase in the number of CFU appears to be incidental to the oncogenic action of the virus at the level of the erythroid precursor cells.

- 0263 VIRUSES FOCUS OF CURRENT CANCER RESEARCH. (E.) Anonymous. *Science* 52(2):16-18, 20, 1974.

Indirect evidence is building in support of the belief that viruses cause cancer in humans. No single virus causes all cancers, but there are candidates for different types of cancer and it may be that no single one by itself is effective. Of the some 600 known animal viruses, about 150 are thought to be oncogenic. They can be divided into 2 major types, one having complete sets of genes composed of DNA; the other, of RNA. Herpesviruses are the DNA viruses most often associated with naturally occurring cancer in animals. Oncogenic viruses are further subdivided by the type of cancer they cause and their morphologic characteristics. Type-B is associated with mammary tumors in mice and monkeys; Type-C with leukemias and lymphomas in vertebrates. Oncogenic RNA virus contains an enzyme, reverse transcriptase, which reverses the usual direction of flow in a cell so that DNA is produced on an RNA template. The technique of molecular hybridization has aided the search for human cancer viruses. Recently evidence of both the presence of particles in human leukemia cells resembling type-C virus RNA and of a link between these and known type-C viruses in animals has been found. Evidence is now available showing that

some human leukemic cells contain a polymerase that has both the biochemical and antigenic properties of reverse transcriptase from known type-C animal viruses and is especially closely related to polymerase of primate type-C virus. So far, the Herpes simplex virus type-1, called Epstein-Barr virus, is the only virus that has been discovered to be associated with certain malignant tumors in man. Recent studies have indicated that an interaction between both RNA and DNA viruses may play a part in the etiology of Burkitt's lymphoma, thus ruling out the idea of a distinct categorization of RNA viruses causing certain types of cancer and DNA viruses causing other types.

- 0264 DETECTION OF COMPLEXES CONTAINING 70S RNA AND REVERSE TRANSCRIPTASE IN HUMAN LEUKEMIC PLASMA. (E.) Yaniv, A. (Inst. Cancer Res., Columbia U., New York, N.Y.), S. C. Gulati, A. Burny and S. Spiegelman. *Intervirology* 1(5-6): 317-328, 1973.

On examining plasmas from 19 leukemia patients and 13 normal blood bank donors, 74% of the leukemic patients showed evidence for the presence of particulate complexes containing 70S RNA and reverse transcriptase. No such complexes were identified in the normal donors. The DNA product synthesized by these complexes hybridized to the RNA of Rauscher leukemia virus and to RNA obtained from leukemic cells and did not hybridize to the RNA of normal leukocytes or to the RNA of the unrelated avian myeloblastosis virus. It is suggested that the levels of these complexes in the plasma may be useful in both diagnosis and treatment.

- 0265 ONCORNAVIRUS TYPE C IN A CONTINUOUS CULTURE OF SWINE EMBRYONIC KIDNEY CELLS (SEKC). (Rus.) Al'tshtein, A. D. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), S. F. Gerasina, L. G. Zakharova, M. V. Sevast'ianova, V. P. Karelin, E. V. Zorin, A. F. Bykovskii, G. G. Miller and V. M. Zhdanov. *Vopr Virusol* (2):222-226, 1973.

Particles isolated from continuous swine embryonic kidney cultures (SEKC) had DNA-polymerase activity when they were incubated with hybrid polyriboadenine-deoxythymidine. They had a density of 1.16 g/ml in a sucrose density gradient and a sedimentation coefficient of about 60 S. Particles which incorporated ^3H -uridine and those containing DNA-polymerase had the same peak density (1.165 g/ml). However, the particles with DNA-polymerase activity contained a larger proportion of material with a density of 1.17-1.21 g/ml than did the particles which incorporated ^3H -uridine. When a purified concentrate of particles was incubated with the 4 deoxynucleoside triphosphates in the presence of either Mg^{++} (0.005 M) or Mn^{++} (0.0002 M), DNA synthesis occurred in 2-3 hr in the absence of a synthetic matrix. Heating for 2 min at 100 C inhibited the reaction significantly. Addition of hybrid polyriboadenine-deoxythymidine did not stimulate DNA synthesis in the presence of Mg^{++} but stimulated it significantly in the presence of Mn^{++} . Electron microscope examination revealed

that these viral particles were identical with type C particles. Particles of immature type C or type A were also present, along with *Mycoplasma*. The particles did not contain the group-specific antigen for murine oncornavirus type C in the gel precipitation or complement-fixation reactions. A diploid modal number of chromosomes (38) was found in SEKC. Although the origin of RNA-containing particles in SEKC is unknown, they probably were introduced into the cultures with the primary explant or may have been activated during prolonged passage of SEKC. In both cases they would be a new swine oncornavirus. It is also possible that these particles may be a contaminant from bovine serum used in the culture medium or cells from another animal species, but this is unlikely in view of the karyotype of SEKC.

- 0266 TRANSFORMATION OF BABOON CELLS WITH FELINE SARCOMA VIRUS. (E.) Melnick, J. L. (Baylor Coll. Med., Houston, Tex.), B. Altenburg, P. Arnstein, R. Mirkovic and S. S. Tevethia. *Intervirology* 1(5-6):386-398, 1973.

Testes cells from two baboons have been transformed by the Snyder-Theilen (ST) and Gardner-Arnstein (GA) strains of feline sarcoma virus (FeSV). The resulting cell cultures formed tumors in immunosuppressed mice, but not in the autologous baboons. The cells transformed by GA FeSV contained more feline gs antigen than those transformed by ST FeSV. Conversely, the cells transformed by ST FeSV produced more type-C virus. Unlike FeSV, which has a predilection for feline cells, the virus from baboon cells transformed by ST FeSV replicated in baboon and beagle embryo cells, but not in feline embryo cells, suggesting that this virus is different from FeSV. These results indicate that baboon cells can be transformed with both ST and GA strains of FeSV. The failure of the cells transformed by either the GA or ST strain to produce tumors may be interpreted in 2 ways. First, the transformed cells may have been rejected by an immune response of the host to surface antigens associated with FeSV-transformed baboon cells. Secondly, the cells, on transformation, may not have acquired oncogenicity.

- 0267 TUMOURS INDUCED IN SHEEP BY INJECTING CELLS TRANSFORMED *IN VITRO* WITH FELINE SARCOMA VIRUS. (E.) Theilen, G. (Chester Beatty Res. Inst., Surrey, England), J. G. Hall, A. Pendry, D. J. Glover and B. R. Reeves. *Transplantation* 17(1):152-155, 1974.

Kidneys were obtained from sheep by unilateral nephrectomy either prenatally or immediately postnatally. Cultures of kidney cells were established. Transformation followed addition of virus material isolated from a feline sarcoma (FeSV). All transformed cells possessed the group-specific antigen of the FeSV but less than 1% of the cells contained intact C-type particles. Injection of autochthonous transformed cells into lambs did not cause tumors to develop. Allogeneic transformed cells, however, induced tumors in 14

of 17 lambs, after a latent period of 6-20 days. In 4 cases where cells from a female line were injected into a male lamb, the tumor cells resulting had a male karyotype and a normal complement of chromosomes, i.e., the tumors had originated from the cells of the host. Of the 14 tumors, 9 spontaneously regressed and 5 grew. Of the 5 which grew, 1 lamb had received 3 mg/kg of cyclophosphamide p.o./day for 4 days after injection and another had received 3 injections of 20 ml horse antishsheep lymphocyte serum during the latent period. It is not known if either of these substances had any substantial immunosuppressive effects. At post-mortem exam of 4 tumors, no cavitation or necrosis was noted, nor any metastatic deposits. The remaining case of progressive tumor growth occurred in a lamb which had been thymectomized *in utero* at 78 days gestation. Six days after receiving the injection of transformed female cells, a tumor was noted, which, after 5 additional days, accounted for 12% of the animal's weight. Again there was no metastatic evidence and the tumor was of host origin. Irrespective of whether tumors formed, all lambs that received transformed cells developed serum antibodies to the group-specific antigen of the virus. It is suggested that the immune response of the host is important in the control of tumor growth.

- 0268 EFFECT OF NONSPECIFIC FACTORS ON FOCUS FORMATION BY ROUS SARCOMA VIRUS. II. POLYANIONS, DIVALENT CATIONS, TEMPERATURE, AND TRYPTOPHOSPHATE BROTH. (E.) Vigier, P. (Inst. Radium Fac. Sci., Orsay, France). *Intervirology* 1(5-6):338-347, 1973.

Formation of foci of Rous cells by Bryan high titer strain Rous sarcoma virus (B-RSV (RAV1)) in chick embryo fibroblast monolayers grown in medium containing agarose and tryptose phosphate broth (TPB) is increased 2-10 fold (or more in crowded cultures) by adding sulfated polyanions (dextran sulfate, or heparin) at the post-infection stage, lowering the concentration of Ca⁺⁺ and Mg⁺⁺ in the medium, or raising the incubation temperature to 41 C. These nonspecific factors may all favor cell transformation by reducing cell adhesion. Heparin was less active than dextran sulfate. Chondroitin sulfate was also tested but was inactive. Dextran sulfate and high temperature also enhanced focus formation by B-RSV (RAV2) but not by PR-RSV(C) or SR-RSV(D). Omission of TPB from the medium reduced 10-100 fold the number of foci produced by B-RSV and 5-10 fold that produced by PR-RSV or SR-RSV. TPB is also required for enhancement by other nonspecific factors of focus formation by B-RSV. Hence, it must act differently from these factors. It is suggested that the response of cells infected with B-RSV to dextran sulfate or high temperature (41 C) depends only on the viral genotype. The temperature experiments show that B-RSV foci can appear by late transformation of infected cells and disappear by reversion of transformed cells to normal phenotype, confirming the observations with RSV ts mutants which show that morphological transformation is reversible.

0269 ABSENCE OF EPSTEIN-BARR VIRAL DNA IN
AMERICAN BURKITT'S LYMPHOMA. (E.)

Pagano, J. S. (U. North Carolina, Sch. Med., Chapel Hill), C. H. Huang and P. Levine. *New Engl J Med* 289(26):1395-1399, 1973.

The cellular DNA from tumor-infiltrated tissue from four patients with the American form of Burkitt's lymphoma did not contain detectable Epstein-Barr viral (EBV) DNA. The analyses were conducted by a highly specific and sensitive molecular hybridization technic, DNA-DNA renaturation kinetics, which can detect 0.4 genome or less of EBV DNA per cell. The absence of nucleotide sequences homologous to the virus in the American lymphomas is in contrast to African Burkitt's lymphoma and also to nasopharyngeal carcinoma, in which EBV DNA is usually detectable even with the less sensitive technic of complementary RNA-DNA hybridization. Six specimens from patients with American Hodgkin's disease and three from patients with metastatic melanoma also did not contain detectable EBV DNA. The apparent absence of viral DNA in the American tumor seems to stand against a role for EBV in American Burkitt's lymphoma. It is suggested that EBV transforms lymphocytes of B-cell origin, both in African Burkitt's lymphoma and in infectious mononucleosis, and that viral DNA persists in these cells. Stimulated by these EBV-bearing B cells, T lymphocytes appear transiently in the circulation. The atypical lymphocytes which do not contain EBV DNA and may be cytotoxic for the virally transformed B cells, herald the protective immunologic response.

0270 RELATIONSHIP BETWEEN THE MECHANISM OF
NATURAL RESISTANCE OF HUMAN EMBRYONIC
CELLS TO ROUS SARCOMA VIRUS AND THE CONDITIONS
UNDER WHICH VIRAL GENOME IS RELEASED IN THE CELLS.
(Rus.) Kuznetsov, O. K. (N. N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR), G. A. Savost'ianov and A. M. Diad'kova. *Vopr Virusol* (4):402-407, 1973.

Rous sarcoma virus (RSV) was treated with cell homogenates and lysosomes from cell cultures which were sensitive or resistant to the virus. The sensitive cultures consisted of skin-muscle tissue from 10-day-old chick embryos and monolayer cell cultures from this tissue, while skin-muscle tissue from 7-12-wk-old human embryos and monolayers of these cells served as resistant cultures. The reaction of the treated virus with pancreatic RNAase (30 µg/ml) was then investigated to establish whether deproteinizing enzymes were present in the different kinds of cells. Untreated RSV, grown in chick embryonic cells, was completely resistant to pancreatic RNAase. Deproteinizing activity was detected after cell homogenates or lysosomes of uninfected cells were treated with detergent (Triton X-100) or were disrupted mechanically. The deproteinizing activity was higher in preparations in which lysosomes had been disrupted with detergent. This can be accounted for by a synergism between the action of the detergent and RNAase with proteolytic enzymes and nucleases present in the preparations tested. The

activity of these deproteinizing enzymes was much greater in sensitive cells than in resistant ones and increased as a result of infection of the cells with RSV. It is suggested that deproteinization of RSV during infection of cells occurs in two stages: (1): hydrolytic enzymes present in the cells disrupt the outer protein membrane and phospholipids in the virus particle and (2) messenger RNA is synthesized by viral DNA-dependent RNA polymerase in the nucleoid which has not yet been released from the protein membrane. This RNA then directs the synthesis of some early proteins, including those that "strip" the virus. Detection of enzymes which deproteinize RSV in the resistant cells suggests that other cellular mechanisms are responsible for species resistance.

0271 SENSITIVITY OF EMBRYONIC CELL CULTURES
FROM DIFFERENT LINES OF MICE AND RATS TO
TRANSFORMATION AND THE CYTOPATHIC EFFECT OF MURINE
SARCOMA VIRUS. (Rus.) Argirova, R. M. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), L. G. Zakharova and A. D. Al'tshtein. *Vopr Virusol* (1):54-59, 1973.

A terminal dilution method was developed for titration of murine sarcoma virus (MSV) in secondary cultures of embryonic mouse cells pretreated with DEAE-dextran (25 µg/ml). Good correlations were obtained between the sensitivity of various mouse and rat lines to the Moloney strain of MSV by this *in vitro* method and by results obtained *in vivo*. Seven of the eight mouse lines tested *in vivo* (C57B1/6, BALB/c, CC57W, CBA, DBA/2y, A/He, CeH/He) had about the same sensitivity to the Moloney strain of MSV, while the AKR mouse line was only 1/10-1/100 as sensitive as the BALB/c line. Wistar rats were 1/100 and August rats 1/1000 as sensitive as BALB/c mice to the Moloney strain of MSV. *In vitro* tests showed that cultures from Wistar rats were 1/15 and those from August rats, 1/200 as sensitive to the Moloney strain of MSV as cultures from mice. The transformation and cytopathic effect produced by the Moloney strain of MSV in embryonic mouse cells was inhibited by anti-MSV sera, and no reaction occurred when cells were pretreated with Rauscher leukemia virus, indicating that these changes are specific for MSV. Cultures of AKR mouse cells were only 1/3 as sensitive to the Gazdar and Moloney strains of MSV as BALB/c and C57B1/6 mice. Rat cells were even less sensitive. The Kirsten strain of MSV, which had been adapted to rat cells, was active only in cultures from Wistar rats and DBA/2y mice.

0272 ISOLATION OF RNA-CONTAINING TYPE C
VIRUSES FROM CONTINUOUS HUMAN CELL
LINES. (Rus.) Zhdanov, V. M. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), N. P. Mazurenko, L. S. Iakovleva, G. N. Trushinskaia and G. K. Gogichadze. *Vopr Virusol* (1):45-50, 1973.

After blocking nuclear synthesis with mitomycin C, RNA-containing viruses were isolated by ultracentrifugation in a sucrose density gradient from contin-

uous cell lines derived from an ovarian carcinoma (CaOv), a solid carcinoma of the gastric antrum (CaVe), and human embryonic skin-muscle cells which had undergone spontaneous transformation. These mature and immature type C particles, which had a density of 1.16-1.17 g/ml, were morphologically identical to those found in murine and avian leukemias, but the dimensions of the human virus particles were somewhat larger. Larger numbers of virus particles were present in the CaOv cell line than in the others. Reverse transcriptase activity was present in the CaOv line. The reaction occurred in the presence of a mixture of the four deoxynucleotide triphosphates, was sensitive to ribonuclease but not very sensitive to actinomycin D, and occurred much more rapidly when synthetic deoxythymidine-polyadenine hybrid was added to the incubation mixture. High-molecular wt RNA, with a sedimentation constant of 67-72 S, and more slowly sedimenting components were obtained from all three viruses when they were treated with 1% sodium dodecyl sulfate and centrifuged in 10-30% sucrose gradients containing 0.5% sodium dodecyl sulfate. Although the viruses isolated may be of human origin, it is possible they may be contaminants from calf serum or swine trypsin which were used in preparing the cell cultures or from mice or birds which are being investigated in the same laboratory. Attempts to isolate RNA-containing viruses from two cell lines derived from angiosarcomas were unsuccessful.

- 0273 HERPESVIRUS TYPE 2-INDUCED THYMIDINE KINASE AND CARCINOMA OF THE CERVIX. (E.)
Rawls, W. E. (Baylor Coll. Med., Houston, Tex.), G. Cashon, E. Adam, T. Ogino, R. Duff, and F. Rapp. *Cancer Res* 34(2):362-366, 1974.

Sera were obtained from 30 women with invasive carcinoma of the cervix, matched control women, patients with cancers of other sites, and a group of laboratory personnel. The sera were examined for neutralizing activity of thymidine kinase induced by herpesvirus type 2. Although inhibition of enzyme activity was found in some of the sera, it appeared to be more related to the patients' past experience with herpesvirus type 2 rather than with the presence or absence of cervical cancer. Thymidine kinase extracted from cervical cancer cells migrated on polyacrylamide gel electrophoresis in a pattern similar to those of the enzymes induced by herpesvirus type 2 in rabbit kidney, rabbit embryo, or Vero cells. The enzyme of the cancer tissue, however, did not appear antigenically related to the virus-induced enzymes.

- 0274 MORPHOLOGY OF ONCORNAVIRUSES TYPES A, B AND C IN CONTINUOUS CELL LINES FROM MAN AND ANIMALS. (Rus.) Bykovskii, A. F. (N. F. Gamaleia Inst. Epidemiol. Microbiol., Moscow, USSR), G. G. Miller, N. V. Klitsunova, L. V. Gorokhova, V. A. Zakhaleva and V. B. Martynenko. *Vopr Virusol* (2):215-221, 1973.

In five yr of morphological research on 50 human and animal cell lines and sublines, oncornavirus

types A, B or C were detected in 26 cell lines. Associations of type A and B virus were observed in 15 human cell lines and of type A and C virus in two human cell lines. Only associations of oncornavirus types A and C were detected in continuous cell lines from monkeys, hamsters, rats, mice and swine. Type A and C virions inside the cells were generally spherical in shape, while some type B particles were polymorphic, particularly in HeLa cells. When they were associated with type B or C particles, type A virions did not constitute more than 10% of the viral population. Type B oncornaviruses were found both in continuous cell lines from human carcinomas and in cell lines of nonmalignant origin (RH, FL, A-1, AO, Detroit-6) which had been cultivated for a long time. It can not yet be ruled out that oncornavirus may result from contamination with animal cells, particularly mouse cells, but this is unlikely in view of the results obtained in detailed karyological analyses.

- 0275 CHARACTERIZATION OF A NEW MURINE CELLULAR DNA POLYMERASE. (E.) Livingston, D. M. (Natl. Cancer Inst., Bethesda, Md.), L. E. Serxner, D. J. Howk, J. Hudson and G. J. Todaro. *Proc Natl Acad Sci USA* 71(1):57-62, 1974.

In the high-speed pellet fraction of 2 subclones of nonvirus producing Balb/3T3 cells, a new DNA polymerase (peak A) has been identified. The activity is associated with a molecule of approximately 70,000 molecular weight and chromatographs in 2 systems like the mouse type-C viral reverse transcriptase and a similar enzyme from the high-speed pellet fraction of a virus producing Balb/3T3 subclone, S₂Cl₃. Comparable quantities of peak A are present in both nonvirus infected (A31) and mouse sarcoma virus transformed nonproducer (KA31) subclones. Virus producing cells contain 10-20 times more peak A polymerase activity. A31 and KA31 peak A are comparably inhibited by anti-mouse type C virus reverse transcriptase IgG but to a lesser degree than S₂Cl₃ peak A or authentic viral reverse transcriptase. They can also be differentiated from the latter 2 enzymes by template preference studies. KA31 peak A can be distinguished from 3 other KA31 DNA polymerases (R-DNA polymerase and DNA polymerase N and C), and thus appears to be a new species of cellular DNA polymerase.

- 0276 RELATIONSHIP BETWEEN RNA-DIRECTED DNA POLYMERASE (REVERSE TRANSCRIPTASE) FROM HUMAN ACUTE LEUKEMIC BLOOD CELLS AND PRIMATE TYPE-C VIRUSES. (E.) Gallagher, R. E. (Natl. Cancer Inst., Bethesda, Md.), G. J. Todaro, R. G. Smith, D. M. Livingston and R. C. Gallo. *Proc Natl Acad Sci USA* 71(4):1309-1313, 1974.

An RNA-directed DNA polymerase was isolated from the peripheral blood leukocytes of a patient with acute myelomonocytic leukemia by successive purification of a particulate cytoplasmic fraction with endogenous, ribonuclease-sensitive DNA polymerase activity. Like RNA-directed DNA polymerase from mammalian type-C virus, the human leukemic cell enzyme efficiently utilized (A)_n·(dT)₁₂₋₁₈ and

(C)_n·(dG)₁₂₋₁₈ and had an approximate molecular weight of 70,000. Further, the leukemic cell enzyme was strongly inhibited by antisera to RNA-directed DNA polymerase from a person with acute myelogenous leukemia. According to these biochemical and immunological data, the leukemic cell enzyme could be differentiated from all other known cellular DNA polymerases but could not be distinguished from the RNA-directed DNA polymerase of primate type-C virus. The data indicate that human acute myelogenous leukemia cells contain components related to the primate type-C virus.

0277 HETEROGENEITY OF HOST GENE TRANSCRIPTION AND TRANSPORT OF HOST RNA TO THE CYTOPLASM IN POLYOMA VIRUS-INDUCED RAT KIDNEY TUMORS. (E.)

Shearer, R. W. (Pacific Northwest Res. Fdn., Seattle, Wash.) and L. A. Mayer. *Biochim Biophys Acta* 335(3):437-440, 1974.

Nuclear and cytoplasmic RNAs from normal kidney and polyoma virus-induced kidney tumors from Wistar-Furth rats were compared by RNA-DNA competitive hybridization. The RNAs from the normal kidneys and kidney nuclei gave identical competition end points, but they lacked species of RNA found in the tumor tissues. This derepression of gene families in the tumor is not due to the transcription of viral genes. The tumor cytoplasmic RNA also contained sequences absent from normal cytoplasmic RNA; again, these were not viral transcripts. The tumor cells had not lost the ability to restrict certain base sequences to the nucleus, the selection of RNAs for transport to the cytoplasm having been altered but not lost. Gene families which were active in the normal kidney were not repressed in the tumor. The tumors induced by the DNA virus differed from chemically-induced hepatomas in the derepression of gene families, although both lacked repression of gene families which are active in normal cells.

0278 INHERITANCE OF SUSCEPTIBILITY AND RESISTANCE TO RAUSCHER LEUKAEMIA VIRUS. (E.) Toth,

F. D. (Inst. Microbiol., U. Med. Sch. Debrecen, Hungary), L. Vaczi and M. Balogh. *Acta Microbiol Acad Sci Hung* 20(3):183-189, 1973.

Inbred Balb/c, DBA/1, and C57Bl/10Sn mice and their F₁ and F₂ hybrids were infected i.p. with a Rauscher leukemia virus suspension. The characteristic course of the resulting illness was progressive in the Balb/c mice and biphasic in the DBA/1 mice, the C57Bl/10Sn mice were resistant. The (Balb/c X C57Bl/10Sn)_{F1} mice showed biphasic leukemia. The (DBA/1 X Balb/c)_{F1} hybrids showed the biphasic course characteristic of the DBA/1 mice, but the degree of splenomegaly was similar to that observed in the Balb/c mice. The (DBA/1 X C57Bl/10Sn)_{F1} hybrids were as resistant as the C57Bl/10Sn parent strain. The susceptibility or resistance of the F₁ hybrids was independent of the direction of the crossing. Among the (Balb/c X C57Bl/10Sn)_{F2} hybrids, the illness was progressive in 20% of the animals and biphasic in 54%; 25% of these animals were resistant. Of the (DBA/1 X Balb/c)_{F2} hybrids,

27% showed a progressive course, 72% showed a biphasic course, and none were resistant. Among the (DBA/1 X C57Bl/10Sn)_{F2} hybrids, none showed a progressive course, 49% showed a biphasic course, and 51% were resistant. Thus, susceptibility to the Rauscher leukemia virus was therefore determined by two genes: Rv-1, which determines susceptibility to the lymphoid leukemia virus; and Rv-2, which determines susceptibility to the spleen-focus-forming virus. On the Rv-1 locus resistance is dominant, while on the Rv-2 locus susceptibility is dominant. The two genes segregate independently of each other. In Rv-2^{S/S} and Rv-2^{S/r} mice, the degree of tumor-specific antibody production is determined by the Rv-1 locus. In the Rv-1^{R/R} and Rv-1^{S/r} mice, interferon production may be a factor determining resistance.

0279 NON-INFECTIOUS INTRACISTERNAL A-TYPE PARTICLES IN A SARCOMA-POSITIVE, LEUKEMIA-NEGATIVE MOUSE CELL LINE TRANSFORMED BY MURINE SARCOMA VIRUS (MSV). (E.) Billiau, A. (Dept. Microbiol., Rega Inst., U. Leuven, Belgium), H. Sobis, H. Eyssen and H. van den Berghe. *Arch Gesamte Virusforsch* 43(4):345-351, 1973.

Transformed cells were derived from a continuous 3T3-type mouse cell line (MO) from germ-free C3H mouse embryo fibroblasts. Normal MO-cells formed contact-inhibited, transparent monolayers of polygonal cells and were highly sensitive to focus induction by Moloney murine sarcoma virus (MSV) and Kirsten MSV. A spontaneously transformed cell line (MO5) induced slowly growing tumors when injected i.m. into mice. Following inoculation of MO cells with Kirsten MSV, two virus-transformed cell lines were isolated: MO-P cells produced infectious MSV and contained extracellular C-type particles; and MO4-cells did not release infectious focus forming virus, but did release infectious MSV upon superinfection with murine leukemia viruses (MLV). Nonsuperinfected MO4-cells contained multiple intracisternal A-type particles. In this respect, these cells differ from the MSV genome-carrying NP-cells, which produce neither particles nor antigen, and from S+L-cells, which release extracellular, noninfectious C-type particles. Since rare A-type particles were also observed in transformed MO and spontaneously transformed MO5 cells, abundant A-type particles in MO4 cells might represent an endogenous virus activated by MSV superinfection.

0280 EXPERIMENTAL HERPESVIRUS INFECTION OF BABOONS (PAPIO CYNOCEPHALUS) AND AFRICAN GREEN MONKEYS (CERCOPITHECUS AETHIOPS) AND RECOVERY OF VIRUS BY TISSUE EXPLANTS. (E.) Eichberg, J. (Microbiol. Infectious Dis. Southwest Fdn. Res. Education, San Antonio, Tex.), S. S. Kalter, R. L. Heberling and M. Brack. *Arch Gesamte Virusforsch* 43(4):304-314, 1973.

Adult African green monkeys and young baboons were inoculated with a baboon-derived herpesvirus (0430) which is antigenically related to herpesvirus SA8. The African green monkeys were not clinically

affected, but herpesvirus 0430 could be isolated from various tissue explants, particularly spleen, for up to 3 weeks following inoculation. In the baboons, the pathogenicity varied with the site of inoculation and was inversely related to age. In intratracheally inoculated newborns and, to a lesser extent, in i.v. inoculated newborns, the virus produced severe illness accompanied by weight loss, anorexia, malaise, dyspnea, and fever. In 2-month-old and 1-year-old baboons, the virus produced no clinical symptoms. In all cases, the recovery of virus from tissue explants was superior to recovery from tissue homogenates using routine methods. New born baboons may be more susceptible to herpesvirus 0430 because of their less well developed immune systems, and there is evidence to indicate that cellular immunity is significant in combating infections caused by enveloped viruses.

0281 STUDIES ON THE PREVALENCE OF ENDOGENOUS TYPE C VIRUS RD 114 IN CATS. (E.) Sarma, P. S. (Nat'l. Cancer Inst., Bethesda, Md.), A. Sharar, J. Tseng, P. J. Price and M. Gardner. *Proc Soc Exp Biol Med* 145(3):757-762, 1974.

Cat cell cultures which were free of demonstrable group-specific (gs-1) antigens of RD 114 virus and feline leukemia virus (FeLV) were tested for the presence of an "inducible" covert type C viral genome. The cultures were of whole embryo, fetal tongue, fetal thymus, osteosarcoma, and adult kidney origin. On the application of 5-iododeoxyuridine (IdU) to the 16 cultures and subsequent cocultivation with human rhabdomyosarcoma (RD) cells, RD 114-like viruses were recovered in infectious form from each of the cultures. FeLV gs-1 antigen was also detected in six cultures derived from different cats, although attempts to isolate an infectious FeLV by passage of culture fluids into feline embryo fibroblast and RD cultures gave inconclusive or negative results. RD 114 virus as well as FeLV were recovered from the spleen and bone marrow of a cat which had previously been found to contain type C virus particles. RD 114-like virus was also isolated from the thymus of a fetal cat which contained RD 114 gs-1 antigen, and many cat lymphosarcoma specimens contained FeLV but no RD 114. These results suggest a widespread prevalence of an inducible RD 114 virus genome in the cat population.

0282 INFECTIOUS MONONUCLEOSIS AND EPSTEIN-BARR VIRUS IN CHILDHOOD. (E.) Tamir, D. (Dept. Pediatrics "A", Rambam U. Hosp., Haifa, Israel), A. Benderly, J. Levy, E. Ben-Porath and A. Vonsover. *Pediatrics* 53(3):330-335, 1974.

The Epstein-Barr virus (EBV) antibody titer was examined in 22 children who were suspected of having infectious mononucleosis (IM) on the basis of 10% or more atypical mononuclear cells in the peripheral blood smears. Blood samples were also taken from a control group of 27 children with other diseases in whom no atypical cells were observed. Paul-Bunnell and mononucleosis tests were negative in all of the suspected IM children, but antibodies

to EBV were demonstrated in 21 of them. Only five children in the control group had antibodies to EBV. Thus, the presence of EBV antibodies with a rising titer supports a diagnosis of infectious mononucleosis. It is of particular importance in children under 1 year of age in whom the finding of atypical mononuclear cells in the absence of positive Paul-Bunnell and mononucleosis tests shows a strong correlation with the EBV antibody titer. This finding frequently occurs in the absence of the typical clinical features of IM.

0283 INDUCTION OF MAMMARY FIBROADENOMAS IN RATS BY ADENOVIRUS TYPE 9. (E.)

Ankerst, J. (Dept. Med. Microbiol., Karolinska Inst., Stockholm, Sweden), N. Jonsson, L. Kjellen, E. Norrby and H. O. Sjögren. *Int J Cancer* 13(3):286-290, 1974.

Newborn Wistar/Furth rats were injected s.c. with adenovirus type 5 or i.p. with adenovirus type 9. Only the adenovirus-9-inoculated animals developed tumors. All of the females developed tumors, the first one being detectable after 14 weeks. No tumors were detectable in the males after 32 weeks. The tumors were single or multiple fibroadenomas which presented in relation to one or several mammary glands. The histological picture with the variations observed corresponded to the picture seen in pericanalicular fibroadenomas in the human female breast. Thus, benign mammary tumors can be induced in rats by a virus and mammary fibroadenomas are induced by adenovirus type 9, which was previously known to be capable of transforming cells *in vitro*.

0284 NUCLEOTIDE SEQUENCES OF RNA TRANSCRIBED IN INFECTED CELLS AND BY *ESCHERICHIA COLI* RNA POLYMERASE FROM A SEGMENT OF SIMIAN VIRUS 40 DNA. (E.) Dhar, R. (Yale U. Sch. Med., New Haven, Conn.), S. Zain, S. M. Weissman, J. Pan and K. Subramanian. *Proc Natl Acad Sci USA* 72(2):371-375, 1974.

The nucleotide sequences of RNA transcribed and accumulated in simian virus 40 (SV40) infected African green monkey kidney cells were analyzed and compared with those derived from *Escherichia coli* RNA polymerase transcripts. The apparent 3' terminus of a major component of the "L"-strand transcript lies very close to a preferred *E. coli* polymerase initiation site on SV40 DNA. This finding suggests that there may be common structural features or interaction of the *E. coli* RNA polymerase initiation sites and sites where transcription terminates or where post-transcriptional cleavage of the RNA occurs.

0285 ONCOGENIC VIRUSES IN THE THROMBOCYTOPENIC STAGE OF EXPERIMENTAL HIPA - PLASMACYTOMA. (E.) Pedio, G. (Inst. Path. Anat. U. Kantonsspital Zurich, Switzerland), J. R. Rüttner, B. Odermatt and D. Gut. *Experientia* 30(3):289-291, 1974.

BALB/c mice of both sexes were inoculated with 1 AE/mouse ultracentrifugate from HIPA tumor ascites, and their platelets counted 1, 3, 8, 10, 13, and 24 days later. On the first and third days after

HIPA inoculation, a thrombocytopenia averaging 6×10^5 platelets was seen. There was no thrombocytopenia on days 8 and 10 after inoculation. Electron microscopic examination of the platelet concentrates and spleens of these mice revealed no virus-like particles. On days 13 and 24 after inoculation, the mice exhibited a relative thrombocytopenia, and by the 24th day, the animals had developed mesenteric tumors with hemorrhagic ascites. Virus particles were found in the spleens of the mice examined on the 13th and 24th days; these particles were of the enveloped A-type lying free in the intercellular spaces and between channels of megacaryocytes or budding at the cytoplasmic membranes. No such particles were found in any of the platelet concentrates. Thus, the virus particles appeared concomitantly with the second thrombocytopenic phase in the development of HIPA tumors.

0286 ABSENCE OF A SPECIFIC GANGLIOSIDE GALACTOSYLTRANSFERASE IN MOUSE CELLS TRANSFORMED BY MURINE SARCOMA VIRUS. (E.) Fishman, P. H. (Nat'l. Cancer Inst., Bethesda, Md.), R. O. Brady, R. M. Bradley, S. A. Aaronson and G. J. Todaro. *Proc Natl Acad Sci USA* 71(2):298-301, 1974.

The composition and metabolism of gangliosides in an established clonal line of mouse-embryo cells, BALB/3T3, were compared with those of a nonproducer subclone transformed by the Kirsten (Ki) strain of murine sarcoma virus (MSV). While the parent cells contained gangliosides GM_3 , GM_2 , GM_1 , and GD_{1a} , the transformed cells contained primarily GM_2 , GM_1 and GD_{1a} being virtually absent. When the cells were grown in the presence of the ganglioside precursor (^{14}C)glucosamine, most of the radioactivity in the BALB/3T3 cells was in GD_{1a} , while over 95% of the label in the transformed cells was associated with GM_2 . Both cell lines contained similar amounts of glucosylceramide, lactosylceramide, trihexosylceramide, and globoside. However, as demonstrated by sensitive radiochemical and enzymological techniques *in vivo* and *in vitro*, the transformed cells contained no detectable $GM_2:UDPGal$ galactosyltransferase activity. Sialyltransferase and N-acetyl-galactosaminyltransferase were unaffected by transformation.

0287 GENETIC ECONOMY OF POLYOMA VIRUS: CAPSID PROTEINS ARE CLEAVAGE PRODUCTS OF SAME VIRAL GENE. (E.) Friedmann, T. (Dept. Pediatrics, Sch. Med., U. California, San Diego). *Proc Natl Acad Sci USA* 72(2):257-259, 1974.

Two-dimensional maps of the nonhistone proteins of purified large-plaque virus were prepared. The distribution of peptides of protein P_1 is similar or identical to that of protein P_2 , which is about half the molecular weight of P_1 . Protein P_3 contains many or most of the same peptides found in P_2 , and about six major new peptides. In addition, several of the peptides seem to be present in reduced amounts compared with P_2 . Most or all of the peptides of P_4 correspond to those found in P_3 , although about 10 to 12 are missing from the lower molecular weight

P_4 . The results suggest that P_1 may be a dimer of P_2 held together through covalent bonding, perhaps a sulfide bond, which resists reduction under the conditions used to prepare samples for gel electrophoresis. The mechanism of the possible proteolytic cleavage which generates product P_4 and P_3 from P_1 or its precursor and the relationship of the cleavage to virus maturation are unknown.

0288 COMPARATIVE STUDIES OF THE VIRUSES RESCUED FROM POLYOMA TUMOR CELL LINES. (E.) Taguchi, F. (Dept. Microbiol., Kitasato U. Sch. Hygienic Sci., Sagami-hara, Japan). *Proc Soc Exp Biol Med* 146(1):254-258, 1974.

The biological properties of a large plaque strain of polyoma virus (St) and two virus strains (R5/2 and R20) isolated from the two St-Lp induced polyoma tumor cell lines, KIT-5/2 and KIT-20W, were studied. In cultures of mouse kidney cells, mouse embryonic cells, and the Swiss 3T3 mouse cell line, the St strain produced only large plaques (St-Lp), R20 produced only small plaques (R20-Sp), and R5/2 produced more than 95% small plaques (R5/2-Sp) and some larger plaques (R5/2-Lp). In the hemagglutination-inhibition (HI) test, the antisera prepared against each of the large plaque viruses reacted almost equally with St-Lp and R5/2-Lp; they also reacted with the small plaque viruses, the HI titer being 1/2 and 1/4 that obtained in the homologous system. The antisera prepared against the small plaque viruses reacted equally with R5/2-Sp and R20-Sp, but reacted little with the large plaque viruses. While the parental strain was highly tumorigenic in newborn CFW and dd mice, R5/2-Lp and R5/2-Sp all showed low tumorigenicity. The cell transforming abilities of R5/2-Sp and R5/2-Lp were also significantly reduced compared to St-Lp when tested *in vitro* in suspensions of hamster embryonic cells.

0289 THE PRESENCE OF THE LUCKÉ HERPESVIRUS GENOME IN INDUCED TADPOLE TUMORS AND ITS ONCOGENICITY: KOCH-HENLE POSTULATES FULFILLED. (E.) Naegelé, R. F. (Lab. Virol., St. Jude Children's Hosp., Memphis, Tenn.), A. Granoff and R. W. Darlington. *Proc Natl Acad Sci USA* 71(3):830-834, 1974.

Tailbud *Rana pipiens* embryos were inoculated with 0.2-0.4 μ l of a suspension containing herpesvirus which had been extracted from a naturally occurring frog renal carcinoma (Lucké tumor). Within 3-8 months, 62% of the surviving tadpoles developed typical, virus-free Lucké tumors of the pronephros and/or mesonephros. Fragments of one of the pronephric tumors were grown in tissue culture and examined by light and electron microscopy. Typical intranuclear inclusions and herpesvirus were detected in the tumor fragment cells maintained at 7.5 C; no inclusions or virus were seen in fragments incubated at 22 C. A second group of tailbud embryos was inoculated with virus extracted from the tumor fragments maintained at 7.5 C, while a third group was inoculated with virus from the cultures maintained at 22 C. Typical Lucké tumors developed in 65% of the group 2 tadpoles,

while none developed among the group 3 tadpoles. With the exception of the "pure culture" requirement, these experiments fulfill the Koch-Henle postulates for the identification of the causative agent of the Lucké tumor.

- 0290 HOMOLOGY BETWEEN BURKITT HERPES VIRAL DNA AND DNA IN CONTINUOUS LYMPHOBLASTOID CELLS FROM PATIENTS WITH INFECTIOUS MONONUCLEOSIS. (E.) Kieff, E. (Dept. Med., U. Chicago, Ill.) and J. Levine. *Proc Natl Acad Sci USA* 71(2):355-358, 1974.

The extent to which Epstein-Barr virus (EBV) DNA sequences are represented by complementary DNA sequences in lymphoblastoid cultures established from patients with infectious mononucleosis (IM) was determined by comparing the reassociation kinetics of labeled EBV DNA in the presence of excess HR-1 lymphoblastoid cell (established from Burkitt tumor biopsy) or Kaplan lymphoblastoid cell (established from patients with IM) DNA. At least 90% of the sequences of purified EBV DNA prepared from HR-1 cells were homologous to the DNA of the herpes virus contained in Kaplan cells. The thermal stability of the homologous and heterologous hybrid DNA molecules could not be differentiated, indicating at least 97% matching of base pairs between the EBV DNA and the herpes viral DNA from the IM patients. Thus, the extent to which differences in the viral genomes could explain the different disease states is limited.

- 0291 STUDIES ON THE RELATIONSHIP BETWEEN DEOXYRIBONUCLEIC ACID POLYMERASE ACTIVITY AND INTRACISTERNAL A-TYPE PARTICLES IN MOUSE MYELOMA. (E.) Wilson, S. H. (Natl. Cancer Inst., Bethesda, Md.), E. W. Bohn, A. Matsukage, K. K. Lueders and E. L. Kuff. *Biochemistry* 13(6):1087-1092, 1974.

The relationship between intracisternal A particles and cellular DNA polymerase activity was studied using extracts from various murine tissues, mouse myeloma cells, and rat hepatoma tissue culture (HTC) cells. The reaction conditions were adjusted for specific measurement of the type of DNA polymerase activity which has been found in isolated mouse A particles. This type of DNA polymerase activity was detected in several A-containing tissues but not in tissues devoid of or containing very low numbers of A particles. Similarly, four enzymes which were isolated from the myeloma cells and which appear to correspond to mouse cellular DNA polymerases were not active under the reaction conditions used for measurement of the A particle associated DNA polymerase. During subcellular fractionation, the enzyme activity behaved as a particulate cytoplasmic component and was concentrated 30-fold in purified A particles relative to the crude homogenate. A similar subcellular distribution was observed for an antigen associated with the primary A-particle structural protein. The DNA polymerase activity cosedimented with A particles in isopycnic sucrose gradients and was not solubilized by treatment with 1 M KCl or several surfactants.

- 0292 CHARACTERISTICS OF MURINE C-TYPE VIRUSES. III. ANTIGENIC CONVERSION AND FOCUS INDUCTION. (E.) Grundner, G. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), E. M. Fenyo and E. Klein. *Int J Cancer* 13(3):412-419, 1974.

Viruses produced by two Moloney lymphoma sublines (Y and Yr) and by hybrids of the Moloney sublines and a mouse L cell subline (YL and YrL) were tested for antigenic conversion and focus induction on JLS-V9 and D56 (S+L-) cells. Two infectivity patterns were observed. Both indicator cell lines were antigenically converted by the Y and YL viruses, whereas only the D56 cells were converted by the Yr and YrL viruses. The Y, Yr, and YrL viruses produced foci on the D56 cells, while the YL virus produced only a few foci in one of three experiments. Similarly, all viruses except YL produced foci on the JLS-V9 cells. Thus, in terms of antigenic conversion, the following patterns were detected (J - JLS-V9 cells; D - D56 cells): Y virus, J+D+; Yr virus, J-D+; and L virus, J+D-. In terms of focus induction on D56 cells the following patterns were seen: Y virus, antigen+ focus+; and YL virus, antigen+ focus-. All five viruses could infect the D56 cells. The viruses produced by the YAC-A9 and YACIR-A9 hybrid cells (YL and YrL) were similar to the viruses produced by each of the lymphoma parents.

- 0293 ISOLATION AND CHARACTERIZATION OF AN ADHERENT, 8-AZAGUANINE RESISTANT VARIANT OF THE BURKITT LYMPHOMA CELL LINE, RAJI. (E.) Nyormoi, O. (Dept. Zool., Indiana U., Bloomington), J. H. Sinclair and G. Klein. *Exp Cell Res* 82(2):241-251, 1972.

A substrate adherent, fibroblast-like cell line (Raji-A) was isolated from a suspension culture of an established Burkitt lymphoma cell line (Raji). Except for the altered morphology associated with substrate attachment, Raji-A is identical to Raji with respect to karyotype, isozyme composition, susceptibility to Epstein-Barr virus (EBV) infection, and inducibility of latent EBV. In order to facilitate fusion experiments with Raji-A, drug resistant variants were induced by treating cells with ethylmethane sulfonate followed by selection in growth medium which contains 8-azaguanine. Three clones (AGRO, AGR3 and AGR6) were found to be resistant to 50 µg/ml of 8-azaguanine. They had only 10-15% as much hypoxanthineguanine phosphoribosyltransferase activity as wild type cells and a low plating efficiency of $1-3 \times 10^{-6}$ in the selective medium, HAT. These variants can be used for studying EBV-lymphoblastoid cell interactions as well as human genetics by cell hybridization.

- 0294 VIRUS-LIKE PARTICLES IN HUMAN MYELOMA WITHOUT PARAPROTEINEMIA. (E.) Tavassoli, M. (Scripps Clinic Res. Fdn., La Jolla, Calif.) and M. Baughan. *Arch Pathol* 96(5):347-349, 1973.

Plasma-like cells derived from smears of bone

marrow aspirate taken from a previously healthy 68-yr-old woman were observed, upon electron microscopic examination, to contain virus-like particles measuring 150 to 220 μ m in diameter. The patient was diagnosed as having multiple myeloma without paraproteinemia. Serum protein studies revealed mild hypogammaglobulinemia but no myeloma spike and only a minute amount of kappa light chain was present in the urine. These findings argue against the hypothesis that virus-like particles in myeloma cells induce the production of myeloma protein. The virus particles were larger than the usual C-type particles and were in the size range of the poxoviruses, suggesting that they may have represented "passenger" viruses finding optimal growth conditions in the milieu of the myeloma cells.

- 0295 ALTERATIONS IN MACROMOLECULAR SYNTHESIS AND CELLULAR GROWTH IN MOUSE EMBRYO FIBROBLASTS INFECTED WITH FRIEND LEUKEMIA VIRUS. (E.) Gabelman, N. (Mount Sinai Sch. Med., City U. New York), W. Scher and C. Friend. *Int J Cancer* 13(3):343-352, 1974.

The effects of Friend leukemia virus (FLV) on macromolecular synthesis, cellular growth, and the cell cycle were studied using secondary mouse embryo fibroblast (MEF-2) cultures. The rate of DNA synthesis in the MEF-2 cultures was increased following infection with FLV compared with control cultures which were untreated or exposed to heat-denatured virus. A peak was reached between 24 and 48 hours after infection. Radioautographic studies revealed that the infected cultures had a higher percentage of cells which incorporated tritiated thymidine into their nuclei as compared with controls. This increase appeared to be independent of the ability of the cells to divide, since it was also observed in infected stationary cultures. The rates of cellular RNA and protein synthesis did not appear to be affected by FLV infection. The time required for the cell population to double was 1/3 shorter in FLV-infected cultures than in control cultures. The shortening of the generation time was due to a decrease in the time required for the cells to traverse the G1 and S phases of the cell cycle. In addition, after 72 hours of growth, the infected cultures reached greater population densities than did either of the controls. It is possible that a structural or enzymatic protein of the virus may mimic, and therefore substitute for, a required cellular protein or that virus infection may result in the derepression of genes coding for proteins required for DNA synthesis.

- 0296 HOMOLOGY BETWEEN HUMAN BREAST TUMOUR RNA AND MOUSE MAMMARY TUMOUR VIRUS GENOME. (E.) Vaidya, A. B. (Inst. Med. Res., Camden, N.J.), M. M. Black, A. S. Dion and D. H. Moore. *Nature* 249(5457):565-567, 1974.

Hybridization experiments were carried out using mouse mammary tumor virus (MuMTV)-specific DNA probes and human breast tumor RNA. Out of 17

tumors tested, five had RNA sequences homologous to the MuMTV genome. When a DNA probe synthesized by Mason-Pfizer monkey virus (MPMV) was used for hybridization under the same conditions, none of the tumors tested showed any RNA sequences homologous to the MPMV genome. All five positive human tumor RNAs showed varied rates of hybridization with the MuMTV DNA probe. The numbers of MuMTV related RNA molecules per cell in the human tumors ranged from 1.5 to 8. With regard to thermal stability, the T_m for hybrids of MuMTV DNA and RNA from RIII lactating mammary gland (a tissue which produces MuMTV) was 69 C compared with 62 C for the hybrids of MuMTV DNA and human tumor RNA. This difference would indicate about 5% mismatching between the MuMTV DNA and the tumor RNA.

- 0297 DETECTION OF ONCORNAVIRUS-LIKE PARTICLES IN HeLa CELLS. I. FINE STRUCTURE AND COMPARATIVE MORPHOLOGICAL CLASSIFICATION. (E.) Gelderblom, H. (Robert Koch-Inst., Berlin, West Germany), H. Bauer, H. Ogura, R. Wigand and A. B. Fischer. *Int J Cancer* 13(2):246-253, 1974.

Electron microscopic examination of HeLa line D cells revealed particles which showed the essential morphological properties characteristic of oncornaviruses. They matured by budding from the cell surface in such a way that fully assembled intracytoplasmic A-type particles were enveloped by the cell membrane with subsequent release of the virion. The core of the mature particle was always condensed and often eccentrically located. The electron-dense nucleoid appeared to be surrounded by an irregularly outlined intermediate shell. Negative staining revealed a rounded shell hiding the viral nucleoid instead of this misformed core shell. The viral envelope was presumably studded with surface projections not longer than 50 angstrom. Some peculiarities in the morphology and synthesis of the HeLa particles distinguish them from all of the known oncornavirus groups of B- and C-type. However, the HeLa particles closely resemble two primate viruses: the Mason-Pfizer monkey virus, and a recently discovered virus derived from human brain cells. Thus, the HeLa virus may be a new type of virus, possibly of human origin.

- 0298 HISTONES STIMULATE POLYRIBONUCLEOTIDE-DIRECTED POLYDEOXYRIBONUCLEOTIDE SYNTHESIS BY MURINE LEUKEMIA VIRUS. (E.) Manly, K. F. (Dept. Med. Oncol., Roswell Pk. Mem. Inst., Buffalo, N.Y.). *J Virol* 13(2):305-311, 1974.

The effects of fractionated and unfractionated calf thymus histones on the rate of homopolyribonucleotide-directed polydeoxyribonucleotide synthesis by the virion-associated DNA polymerase of Moloney murine leukemia virus (MLV) were studied. The rate of homoribopolymer-directed DNA synthesis by detergent-disrupted MLV could be either stimulated or inhibited by the unfractionated histone, depending on the ratio of histone to template. Of the fractions which can be separated

from the whole histone, fl caused both the greatest stimulation and the greatest inhibition. The effect of this fraction was qualitatively similar with polyadenylate (poly A), polycytidylate, or polyuridylate as template, the stimulation being greatest with poly A. The pattern of stimulation and inhibition differed with the DNA polymerase of *Micrococcus luteus*, which was inhibited by histone concentrations which stimulated the viral enzyme and stimulated by concentrations which inhibited the viral enzyme. For the viral enzyme, the optimum histone concentration was unaffected by changes in the virus or primer concentration. However, it varied in proportion to the template concentration, suggesting that the histone acts by combining stoichiometrically with the template. The data raise the possibility that a histone-like protein may participate in the synthesis of the provirus of RNA tumor viruses.

0299 PROPOSAL FOR NUMBERING MUTANTS OF AVIAN LEUKOSIS AND SARCOMA VIRUSES. (E.)

Vogt, P. K. (U. Southern California Sch. Med., Los Angeles), R. A. Weiss and H. Hanafusa. *J Virol* 13(2):551-554, 1974.

A convention for designating and numbering the mutants of avian leukosis and sarcoma viruses is proposed. Each laboratory isolating conditional or nonconditional mutants of these viruses would select two capital letters which would be listed, preferably in italic type, before the mutant number. Investigators could assign any number to new mutants isolated in their laboratory; such numbers could include lower-case Greek letters. If necessary, a suitable abbreviation of the mutant category would be incorporated in the designation of each mutant. This would consist of lower-case italic letters placed without a hyphen before the laboratory code letter. An abbreviation of the wild-type strain would follow the mutant number when required. The envelope subgroup might be appended, by using a hyphen, as a capital Roman type letter to the mutant number or wild-type strain designation. If a second mutation were introduced in a mutant virus, a supplementary number would be attached to the first mutant number by using a hyphen.

0300 EARLY CHROMOSOME CHANGES IN DIPLOID CHINESE HAMSTER CELLS AFTER INFECTION WITH SIMIAN VIRUS 40. (E.) Lehman, J. M. (U. Colorado Med. Sch., Denver). *Int J Cancer* 13(2):164-172, 1974.

Confluent cultures of primary and secondary Chinese hamster embryo cells and primary mouse cells were infected with the RH-911 strain of simian virus 40 (SV40). Chromosome preparations were then made from cells which had been treated with colcemid. The SV40-infected hamster cells exhibited chromosomal changes within one cell generation (24 hours). The initial change was an increase in the number of polyploid metaphases (>10%). The majority of the polyploid cells were tetraploid

(8X) although higher ploidy values were also observed (16X, 32X, and 64X). In approximately 20 to 30% of the polyploid metaphases there were chromosome changes such as breaks, abnormal chromosomes, and missing or additional chromosomes. The remaining polyploids were normal with regard to chromosome number and morphology. The SV40-infected mouse embryo cells also showed an increase in the number of polyploid cells within 48 hours.

0301 PROPERTIES OF FLAT VARIANTS OF MURINE SARCOMA VIRUS TRANSFORMED NON-PRODUCER CELLS ISOLATED AFTER HIGH-TEMPERATURE PASSAGE. (E.) Gazdar, A. F. (Nat'l. Cancer Inst., Bethesda, Md.), H. B. Stull, H. C. Chopra and Y. Ikawa. *Int J Cancer* 13(2):219-226, 1974.

Subclones of the clonal lines BALB/3T3 and its Kirsten murine sarcoma virus (MSV)-transformed subclone K-234 (K/3T3T and K/3T3I, both nonproducer lines) were adapted to high temperature (40.5 C) by passages at intermediate temperatures. High-temperature passage increased the incidence of flat variants obtained from K/3T3 from less than 0.1% to 4%. The flat variants had growth characteristics similar to those of BALB/3T3 line. The variant lines did not release detectable type C virus, but some contained intracisternal type A particles. Super-infection of the variants with murine leukemia virus (MuLV) resulted in retransformation and the release of sarcoma virus. Some of the variant lines may be suitable indicator cells for the assay of MuLV. The modal chromosome numbers of the variant lines were considerably higher than those of their progenitor cell line.

0302 VIRUS-SPECIFIC MESSENGER RNA ON FREE AND MEMBRANE-BOUND POLYRIBOSOMES FROM CELLS INFECTED WITH RAUSCHER LEUKEMIA VIRUS. (E.) Gielkens, A. L. J. (Dept. Biochem., U. Nijmegen, The Netherlands), M. H. L. Salden and H. Bloemendal. *Proc Natl Acad Sci USA* 71(4):1093-1097, 1974.

Cells which are infected by Rauscher leukemia virus synthesize virus-specific RNA which can be detected by hybridization to the single-stranded DNA copy of the viral RNA. The JLS-V9 cell line, derived from bone marrow cells of BALB/c mice, infected with and producing Rauscher leukemia virus, was grown. It was found that virus-specific RNA was present in free and membrane-bound polyribosomes of these cells. The relative content of virus-specific RNA, as measured by hybridization, was 6-10 times less on free polyribosomes than on membrane-bound polyribosomes. The messenger RNA associated with both classes of polyribosomes was characterized by density gradient centrifugation. In addition to a major RNA species identified as 36S RNA, at least 2 minor components in the 14S and 21S region were found. There is a striking difference in the distribution of these RNA species between free and membrane-bound polyribosomes.

0303 ELECTRON MICROSCOPIC STUDIES ON SIALOGLYCOPROTEIN LAYER OF RAT FRIEND TUMOR CELLS. (E.) Kodama, T. (Cancer Inst., Hokkaido U., Japan), N. Takeichi, E. Gotohda and H. Kobayashi. *Gann* 64(6):613-616, 1973.

The colloidal iron-stained sialoglycoprotein layer on the cell surface of three different lines of transplantable Friend virus-induced tumors in Wistar-King-Aptekman rats which showed different growth patterns in the host rats was studied under the electron microscope. The thickness of the iron-stained layer on the cell surface was related to the growth pattern of the tumors. The sialoglycoprotein layers on the cell surfaces were highly stained in WFT-2N cells which showed lethal growth in normal syngeneic rats, moderately stained in WFT-2A cells, which showed temporary growth, and weakly stained in WFT-3 cells which showed no growth. It has been suggested that the cell surface sialic acid may mask tumor cell antigens, and consequently inhibit the host's immunological mechanisms by preventing antigen detection. Therefore, tumor cells rich in sialoglycoprotein show rapid growth, invasion, and metastasis.

0304 THE IMPORTANCE OF DOSE AND PROLIFERATION OF SV40-TRANSFORMED CELLS WITH DIFFERENT ONCOGENIC POTENTIALS TO THE LEVEL OF TUMOR IMMUNITY. (E.) Stillström, J. (Dept. Virol., U. Uppsala, Sweden). *Int J Cancer* 13(3):273-285, 1974.

The immunizing effects of syngeneic Simian virus 40 (SV40)-transformed mouse embryo cells derived from a cloned line (MEi C9) were studied. The 50% immunizing dose (ImD_{50}) of highly oncogenic MEi C9-V15 cells against a weak challenge 3 weeks after immunization was $10^{4.1}$ irradiated or $10^{2.7}$ nonirradiated (proliferative) cells. Doses just below the ImD_{50} suppressed immunity. An immune state was reached more rapidly after resection of tumors induced by 10^2 cells, even when the resections were performed at a time when the animals were still nonimmune. The immune suppression induced by a low dose of nonirradiated cells seemed to be perpetuated and 10 weeks after inoculation there was still an immune deficit in comparison with the state of immunity in animals which had had their tumors resected. A second inoculation of a regularly nonimmunizing dose of 10^1 - 10^2 cells 3 weeks after inoculation of 10^2 cells enhanced the tumor incidence of the first inoculated cells. After inoculation of 10^5 irradiated or nonirradiated cells, a 1000-fold increase in tumor resistance was obtained in 3 weeks. Before reaching a size of 12 mm, the tumor mass did not affect the level of immunity. Tumor resections 3 weeks after inoculation of 10^5 cells preserved the otherwise declining immunity. The ImD_{50} s of weakly oncogenic and highly oncogenic nonirradiated cells in irradiated animals against a weak challenge 10 weeks after immunization were $10^{2.6}$ and $10^{1.5}$ cells, respectively, in tumor-free animals. Immunization doses of 10^1 - 10^2 weakly oncogenic cells enhanced

challenge tumor takes. Non-tumor-bearing animals inoculated with weakly oncogenic cells were less immune than non-tumor-bearing animals inoculated with highly oncogenic cells, and animals with tumors induced by weakly oncogenic cells were less immune than animals with tumors of comparable size induced by highly oncogenic cells. The critical tumor size at which immunity against 10^5 cells was broken was 11-12 mm for highly oncogenic cells and less than 4 mm for weakly oncogenic cells.

0305 EVIDENCE FOR ALLOSTERISM IN *IN VITRO* DNA SYNTHESIS ON RNA TEMPLATES. (E.) Cavallieri, L. F. (Sloan Kettering Inst. Cancer Res., Rye, N. Y.), M. J. Modak and S. L. Marcus. *Proc Natl Acad Sci USA* 71(3):858-862, 1974.

Hemoglobin mRNA and $(\text{rA})_n \cdot (\text{dT})_{10}$ have been used as primer-templates in a kinetic study of DNA synthesis with *Escherichia coli* DNA polymerase I (DNA nucleotidyl transferase) and Mason-Pfizer monkey virus reverse transcriptase (RNA-directed DNA polymerase). The rate versus enzyme concentration curve is sigmoidal and is consistent with a cooperative phenomenon. The results may be interpreted in terms of the formation of an active complex containing enzyme dimers (or oligomers) on the primer-template. Sigmoidal kinetics were also observed in rate versus deoxynucleotide triphosphate concentration. These results are consistent with an allosteric mechanism in which the triphosphates act as both modifiers and DNA precursors. In the critical range, a 6- to 8-fold increase in both enzyme and triphosphate concentrations can lead to a 1500-fold increase in the rate of synthesis on an RNA template. Thus, small changes in enzyme and precursor concentrations could play a regulatory role *in vivo*.

0306 ONCORNAVIRUS-LIKE PARTICLES IN HeLa CELLS. II. IMMUNOLOGICAL CHARACTERIZATION OF THE VIRUS. (E.) Bauer, H. (Robert Koch-Inst., Berlin, West Germany), J. H. Daams, K. F. Watson, K. Mölling, H. Gelderblom and W. Schafer. *Int J Cancer* 13(2):254-261, 1974.

The immunological characteristics of an oncornavirus-like agent which has been isolated from HeLa cells of human origin were studied by immunodiffusion and gel electrophoresis. The pattern of the major protein constituents of the HeLa virus was similar to that of known oncornaviruses (avian myeloblastosis virus and murine leukemia virus (MuLV)). Six polypeptides with molecular weights (mw) between 12,000 and 28,000 daltons and two glycopolypeptides with mw of about 60,000 to 80,000 daltons were detected by SDS-polyacrylamide gel electrophoresis. No serological cross-reaction was found between the HeLa virus and B- (mammary tumor virus and avian oncornaviruses) and C-type (MuLV and feline leukemia virus) oncornaviruses. Essentially, none of two interspecies-specific antigen determinants described in mammalian C-type viruses was detected in the HeLa

virus. However, a distinct serological relationship was found between the HeLa virus and the Mason-Pfizer monkey virus in that these viruses share at least two antigens in the MW range of 16,000 and 28,000 daltons, respectively. Thus, the HeLa virus appears to be oncornavirus-like but structurally distinguishable from the classical B-type and C-type particles. These results provide further evidence for the existence of a new group of oncornavirus-like particles.

- 0307 FUSION OF A ROUS SARCOMA VIRUS TRANSFORMED HUMAN CELL LINE, KC, BY RD-114 VIRUS. (E.) Rand, K. H. (Natl. Cancer Inst., Bethesda, Md.) and C. W. Long. *J Gen Virol* 21(Pt. 3):523-532, 1973.

RD-114 virus rapidly induces fusion of the KC cell line, a human malignant glioma cell transformed by Rous sarcoma virus. Treatment of the virus with trypsin, heat, ultrasonic vibration, or ether, completely eliminated fusion activity, while deoxyribonuclease, ribonuclease, or neuraminidase treatment had no effect. β -Propiolactone destroyed completely the infectivity of the virus but caused no decrease in fusion activity. Treatment of normal KC cells with actinomycin C, cytosine β -D-arabinofuranoside, or cycloheximide did not prevent fusion in response to the virus. The results indicate that intact, but not necessarily infectious RD-114 virus is required for fusion. When KC cell cultures were fused by RD-114 virus and were transferred repeatedly, they were gradually overtaken by small, unfused KC cells and the large multinucleate cells disappeared. The RD-114 virus which was produced by such cultures was no longer capable of inducing fusion until after it had been passaged again in RD or human embryonic fibroblasts. It was suggested that the apparent recovery of fusion activity by the virus could have resulted from a host cell contribution to the outer surface of the virus.

- 0308 VIRUS-LIKE PARTICLES OBSERVED IN NORMAL TISSUES AND ADENOVIRUS 12-INDUCED TUMORS IN HAMSTERS. (E.) Ohtsuki, Y. (Okayama U. Med. Sch., Japan), K. Matsuo, M. Ohmori and K. Ogawa. *Gann* 64(6):609-612, 1973.

One tenth ml of adenovirus type 12 was inoculated s.c. or i.p. or instilled nasally into newborn Syrian hamsters. Eight primary tumors which developed within 40 to 80 days were then examined, as were 4 lung tumors and 12 brain tumors which had been derived from a primary adenovirus 12 tumor and transplanted into hamsters. Virus-like particles having a diameter of 90-110 nm and three layers with radial nucleoids were occasionally observed in the primary adenovirus 12 induced tumors as well as in the normal lung and brain tissues of uninoculated newborn hamsters. Similar particles were observed in large numbers in the transplanted tumor cells. The particles were generally found in the rough-surfaced endoplasmic reticulum, and intranuclear particles along with intracisternal budding were also observed. The data suggest that a state of coexistence and coprosperity may have existed between the tumor cells and the virus-like particles.

- 0309 MAMMALIAN CELLS IN CULTURE FREQUENTLY RELEASE TYPE C VIRUSES. (E.) Lieber, M. M. (Natl. Cancer Inst., Bethesda, Md.), R. E. Benveniste, D. M. Livingston and G. J. Todaro. *Science* 132(4107):56-59, 1973.

Many commonly used mammalian cell cultures from various species (e.g., mouse, cat, pig, rat, hamster) produce readily detectable amounts of type C RNA viruses with biochemical and immunologic properties similar to those of known leukemia and sarcoma producing viruses. Virus production occurs from cell strains and continuous cell lines of different morphologic types and different degrees of differentiation (e.g., connective and hematopoietic tissue, and cells secreting steroid hormones). The virus release can begin spontaneously after hundreds of cell generations *in vitro*; since these viruses have been unable to infect any of a variety of nonproducing mammalian cells, it is unlikely that they were introduced into the producing cultures by inadvertent laboratory contamination. The virus production has not resulted in cytopathic alterations in the producing cells. Each of the virus-producing cell lines was positive for the type C virus mammalian interspecies group specific antigen. These endogenous type C viruses must be regarded as potential biohazards to laboratory personnel involved in handling producing cells.

- 0310 ONCOGENIC MORPHOLOGY AND MORPHOGENESIS OF AN RNA-CONTAINING VIRUS (STRAIN LPV) ISOLATED FROM MAN IN HUMAN CELL CULTURES. (Rus.) Andzhaparidze, O. G. (Moscow Sci. Res. Inst. Viral Preparations, USSR), V. D. Lotte and L. G. Stepanova. *Vopr Virusol* (1):36-38, 1973.

An electron microscope study was made of an oncornavirus (strain LPV) in the 69th, 80th, 83rd and 105th passages of the transformed human cell line T-9 and in the 13th passage of a newly transformed culture obtained by infecting a human diploid cell culture (strain L-58) with a viral fraction having a buoyant density of 1.16-1.17 g/ml in a sucrose density gradient. The virus was morphologically identical with viruses of the mammalian leukemia-sarcoma complex. Mature and immature type C particles were present on the cell surface and in the extracellular space. These virions were formed by budding on the cell surface with simultaneous differentiation of all the viral structures (membrane, viroplasm and nucleoid). Immature type C particles consisted primarily of oval particles measuring $(110 \pm 10) \times (80 \pm 5)$ nm, but some strands were also found which contained the cylindrical nucleoid and reached a length of 800 nm. Mature type C virions, which also formed on the cell surface, were apparently an independent morphological variant of the virions and were not morphogenetically related to the immature type. The overwhelming majority of virions were immature type C particles. Type A particles were observed singly or in large clusters in the cytoplasm and cisternae. Intracytoplasmic type A particles were oval with diameters of $(70 \pm 10) \times (50 \pm 5)$ nm and were nucleocapsids of intracisternal type A particles. The intracisternal type A particles formed on the walls of vacuoles in the presence of nucleoids which had been produced earlier. No type

B particles were found in any of the preparations examined.

0311 BIOPHYSICAL PROPERTIES OF VIRIONS AND SUBVIRAL COMPONENTS OF TYPE B ONCORNAVIRUS.

(*Rus.*) Bukrinskaia, A. G. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), L. V. Agafonova, A. F. Bykovskii, K. V. Il'in and V. M. Zhdanov. *Vopr Virusol* (3):384-389, 1973.

Type B oncornavirus, obtained from a transplanted line of human tumor cells, was grown in HEp-2 cells labeled with ^3H -uridine and purified as described earlier. Subviral components were obtained by treating virions with a 0.5% solution of nonionic detergent (NP-40). By using ^{32}P -labeled Sendai virus as a marker, virions of type B oncornavirus were shown to have a sedimentation constant of 400-500 S and a density of 1.17-1.18 g/ml in a sucrose density gradient and 1.21 g/ml in a cesium chloride density gradient. Subviral components of type B oncornavirus sedimented more slowly than those of Sendai virus. After treatment with nonionic detergent and centrifugation in a cesium chloride density gradient, two subviral components were isolated: one with a buoyant density of 1.27 g/ml and another with a buoyant density of 1.31 g/ml. Electron microscope examination of oncornavirus virions revealed that they had diameters of 90-100 nm. The fraction with a buoyant density of 1.27 g/ml consisted of spherical structures with diameters of 30-40 nm and no outer membrane (nucleoid), while that with a buoyant density of 1.31 g/ml consisted of nucleocapsid strands about 2.5 nm thick which, in some cases, contained pseudospirals with diameters of 6-8 nm.

0312 QUANTITATION OF BOVINE PAPILLOMA VIRUS AND SERUM ANTIBODY BY IMMUNODIFFUSION.

(*E.*) Koller, L. D. (Nat'l. Inst. Environmental Health Sci., Research Triangle Park, N.C.), S. W. Barthold and C. Olson. *Am J Vet Res* 35(1):121-124, 1974.

A modified micro-Ouchterlony immunodiffusion technique was used to determine bovine serum antibody titers to bovine papilloma virus, and a radial immunodiffusion technique was used to quantitate the virus. The tests were simple to perform, required small amounts of antigen and antiserum, and were more sensitive than the qualitative Ouchterlony method. Sera from calves having naturally occurring infections had lower antibody titers than were seen in sera from calves with experimentally induced papillomas or s.c. papillomatous cysts. Naturally occurring papillomas from calves had higher antigen titers than did experimentally induced papillomas.

0313 ISOLATION AND CHARACTERIZATION OF A RABBIT FIBROMA VIRUS FROM A NATURALLY OCCURRING TUMOR. (*E.*) Kasza, L. (Coll. Vet. Med., Ohio State Univ., Columbus). *Am J Vet Res* 35(1):87-89, 1974.

A rabbit fibroma virus was isolated from a naturally occurring tumor in a wild cottontail rabbit. After three or more passages in rabbit kidney cell culture,

the virus produced a marked cytopathic effect (CPE). Intracytoplasmic inclusions were seen which stained green with acridine orange stain and red with Feulgen reaction, indicating the accumulation of DNA. The isolate was neutralized with homologous antiserum. In cell culture preparations, the viral particles measured 220 nm by 250 to 270 nm in diameter. When the cell cultured virus was inoculated into young, white, domesticated rabbits, neoplastic growths appeared at the site of inoculation; these growths diminished in size after the seventh day. By the seventh day, the growths microscopically resembled the original tumor.

0314 ULTRASTRUCTURAL EFFECTS OF THYMIDINE ANALOGS ON MELANOSOMES AND VIRUS ACTIVATION IN CLONED HAMSTER MELANOMA CELLS IN CULTURE. (*E.*)

Epstein, W. L. (U. California Sch. Med., San Francisco), K. Fukuyama and T. E. Drake. *Yale J Biol Med* 46(5):471-481, 1973.

Two clones of hamster melanoma cells, one having full melanization potential and the other being a poor producer of R-type virus, were exposed in culture to 5-bromodeoxyuridine (BrdUR) or 5-iododeoxyuridine (IdUR) for 48 hr and then washed and grown in fresh media for 4-8 days. After some initial cell death, the surviving cells grew well. All of the treated cells became more lightly pigmented than the controls. Ultrastructurally, while premelanosomes appeared prominently in the cells, the development of melanosome complexes, and autophagosomes was curtailed, especially in the IdUR-treated cells and in the pigmented (MB) cell line. At the same time, many lamellated bodies (lysosomes) were found in the cells and lamellated structures occurred in the premelanosomes. These data suggest a differential effect of thymidine analogs on the dual system controlling melanogenesis in these melanoma cells. Pigment progression, leading from premelanosomes to melanosome complexes is blocked, while the interruption of melanogenesis associated with the appearance of lamellated structures within the pigmentary bodies continues. R-type virus was seen in the BrdUR-treated cells in high concentrations, but was not seen in the IdUR-treated cells. The virus appeared morphologically typical and remained in the rough endoplasmic reticulum. Virus formation did not seem to be correlated with pigment synthesis.

0315 ANTICOAGULANTS AS INHIBITORS OF REVERSE TRANSCRIPTASE ACTIVITY. (*E.*) Kiehl, B.

L. (Dept. Biol., Western Michigan U., Kalamazoo), P. B. Stott, A. C. Huang and D. A. Buthala. *J Nat'l Cancer Inst* 51(5):1705-1707, 1973.

Blood samples from a number of patients with symptoms of diverse malignant diseases were collected in vacutainers containing heparin, ethylenediaminetetraacetate (EDTA), glass beads, or citrate-phosphate-dextrose solution (CPD). The plasma was then separated from these samples and murine Rauscher leukemia virus was added to the plasma. Plasma collected by glass bead defibrination, CPD, or EDTA inhibited reverse transcription to a lesser extent than did that collected in heparin. A dilution of the heparinized

plasma to less than 1:1000 was required to eliminate the inhibition. Heparin added to the reverse transcriptase reaction at 0, 5, or 15 min of incubation caused an immediate incorporation plateau. The DNA product formed before the addition of heparin was not degraded during the observation period.

- 0316 INFECTIOUS DNA FROM HERPES SIMPLEX VIRUS: INFECTIVITY OF DOUBLE-STRANDED AND SINGLE-STRANDED MOLECULES. (E.) Sheldrick, P. (Inst. Sci. Cancer Res., C.N.R.S., Villejuif, France), M. Laithier, D. Lando and M. L. Ryhiner. *Proc Natl Acad Sci USA* 70(12):3621-3625, 1973.

The infectious units in native and alkali-denatured preparations of herpes simplex virus DNA were characterized with respect to their sensitivity to *Neurospora crassa* endonuclease, their sedimentation properties in high-salt, neutral sucrose gradients, and their sensitivity to hydrodynamic shearing forces. Infectious molecules in native preparations were resistant to *N. crassa* endonuclease, sedimented at 56 S, and were highly sensitive to shearing forces. After alkaline denaturation, the molecules maintained infectivity but became sensitive to the *N. crassa* enzyme, sedimented at 200 S, and were relatively resistant to shear. The properties of the native preparation served to characterize the intact infectious unit as a duplex DNA molecule with a molecular weight $\approx 100 \times 10^6$ daltons; those of the denatured preparation were consonant with an intact infectious DNA strand with a molecular weight $\approx 50 \times 10^6$ daltons. The findings suggest that the usual definition of "intactness" in DNA strands may be supplemented by a requirement of genetic information which is necessary and sufficient for productive viral replication, as exemplified by the infectiousness of single stranded herpes simplex virus DNA.

- 0317 ULTRASTRUCTURE OF A POLYOMA-INDUCED SARCOMA DURING ITS GROWTH IN RAT KIDNEYS. (Ger.) Georgii, A. (Med. Coll., Hannover, Germany), J. Thiele and E. Reale. *Z Krebsforsch* 80(4):255-264, 1973.

Renal sarcomas were induced in Wistar-AF/Hannover rats by s.c. injection of SE-polyoma virus 1530 within 24 hr after birth. These tumors were examined under the electron microscope to determine from which cells these tumors originate, whether any differentiation in the ultrastructure occurs during tumor growth, and whether the tumor cells contain viral particles. Tumors were examined 20-102 days after injection of the virus. The sarcoma consisted of a single type of cell that was consistent with a fibroblast because it synthesized collagen and elastic fibers. The matrix cell of the sarcoma was an interstitial cell of the fibroblast type located at the boundary between the renal cortex and medulla. Because of the very large number of capillaries in the sarcoma and the pericapillary location of the first detectable sarcoma cells, the tumors could have originated from pericytes, but no evidence of pericytes or hemangiopericytomas was found under the electron microscope. The possibility that the sarcomas

originated from undifferentiated mesenchymal cells in the interstitial tissue of the kidney was also ruled out. The same ultrastructure was found in all sarcoma cells, regardless of the age of the animal. This ultrastructure was also observed in cells of a polyoma-induced sarcoma in a rat which had undergone thymectomy shortly after birth and in tissue cultures of polyoma-induced sarcoma. The number of collagen fibers increased continuously until the 40th day; after 50-80 days a relative decrease had occurred in the number of tumor cells because of the increase in the number of collagen fibers. No particles of polyoma virus were observed in sarcoma cells, other cells, or in the ground substance of the tumor.

- 0318 PARTIAL PURIFICATION OF INTRACELLULAR MURINE SARCOMA-LEUKEMIA VIRUS RNA SPECIES BY MEMBRANE FILTRATION. (E.) Tsuchida, N. (St. Louis U. Sch. Med., Mo.), S. Bhaduri, H. J. Raskas and M. Green. *Intervirology* 1(1):27-33, 1973.

Both 35S and 20S viral RNA species from transformed rat embryo fibroblasts which produce the murine sarcoma-leukemia virus complex were retained on nitrocellulose membrane filters. The binding and elution from Millipore filters resulted in a 33-fold enrichment for virus-specific RNA, the binding of viral RNA was linear in the range tested, and 54% of the virus-specific RNA was recovered by this procedure. The data indicate that both the 35S and 20S intracellular viral RNAs contain poly(A) tracts.

- 0319 PUBLIC HEALTH IMPLICATIONS OF MAREK'S DISEASE VIRUS AND HERPESVIRUS OF TURKEYS. STUDIES ON HUMAN AND SUBHUMAN PRIMATES. (E.) Sharma, J. M. (Frederick Cancer Res. Ctr., Frederick, Md.), R. L. Witter, B. R. Burmester and J. C. Landon. *J Natl Cancer Inst* 51(4):1123-1128, 1973.

Cynomolgus, rhesus, and bonnet monkeys inoculated with high doses of herpes-virus of turkeys (HVT) or pathogenic Marek's disease virus (MDV) were observed for 11-31 months. None developed detectable viremia, hematologic abnormalities, or clinical disease. Sera from 3 of 12 monkeys inoculated with HVT reacted against HVT antigen in an immunofluorescence (IF) test, whereas all 8 MDV-inoculated monkeys remained negative. Approximately 15 months after initial inoculation, 1 reactor and 1 nonreactor monkey from the HVT-inoculated group were given a second injection of cell-associated HVT propagated in duck embryo fibroblast (DEF) cells. One reactor and 1 nonreactor from the same group received normal DEF cells. Virus-inoculated animals developed IF reactions against HVT, but the 2 animals inoculated with normal DEF cells remained negative. Sera from people in 7 different categories, including those with prolonged contact with HVT and MDV, were tested by IF test for HVT and MDV antibody. Of approximately 200 sera, 8% had IF reactions. There was no apparent correlation between the extent of contact with the 2 viruses and the incidence of IF reaction. Of 25 sera from Burkitt's lymphoma patients, 1 serum had a weak (1:5) reaction against MDV antigen. Human and monkey sera positive by the IF test lacked specific virus neu-

tralizing activity. The significance of IF reaction, therefore, remained unclear. These data supported earlier findings and provided additional circumstantial evidence that MDV and HVT do not constitute a public health hazard.

0320 AVIAN MYELOBLASTOSIS VIRUS INFECTION, BIOSYNTHESIS OF HEAVY POLYSOMAL, RAPIDLY LABELED RNA, AND CELL DIFFERENTIATION. (Fr.) Verger, C. (Gustave Roussy Inst., Villejuif, France), J. Imbenotte, E. Delain and J. Harel. *Biochimie* 56(3):373-381, 1974.

0321 THE DETECTION OF ONCORNAVIRUSES IN CONTINUOUS TISSUE CULTURES. (Rus.) Zhdanov, V. M. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), A. F. Bykovskii, A. D. Al'tshtein, T. F. Lozinskii, L. V. Uryvaev, M. L. Volkova, F. I. Ershov, K. V. Il'in, T. A. Bektemirov, I. S. Irlin, G. G. Miller, L. G. Zakharova, V. V. Perekrst, C. F. Gerasina and M. V. Sevast'ianova. *Vopr Virusol* (4):411-415, 1973.

0322 CYTOLOGICAL CHANGES IN HERPES GENITALIS. (Ger.) Schneider, M. L. (Inst. Clin. Cytol., Technical U., Munich, Germany). *Geburtschilfe Frauenheilkd* 33(7):576-580, 1973.

0323 STUDY OF THE PATHWAYS FOR INTRAUTERINE TRANSMISSION OF HERPES SIMPLEX VIRUS IN EXPERIMENTS ON RABBITS. (Rus.) Slepova, O. S. (G. Hel'mholz Sci. Res. Inst. Eye Dis., Moscow, USSR), N. S. Zaitseva and T. V. Murav'eva. *Vopr Virusol* (2):151-156, 1973.

0324 ISOLATION OF LEUKOVIRUS FROM CELL LINES FROM THE LYMPH NODES OF CALVES. (Rus.) Zhdanov, V. M. (No affiliation), M. I. Parfanovich, F. I. Ershov, T. A. Nikol'skaia, N. F. Kazak, S. D. Nitavskaia, L. I. Nagaeva and R. A. Kukain. *Veterinariia* (4):45-46, 1974.

0325 ANALYSIS OF PROTEINS IN TYPE B ONCORNAVIRUSES PRODUCED BY CELL CULTURES OF HUMAN LARYNGEAL CARCINOMA HEP-2. (Rus.) Zaretskii, I. Z. (D. I. Ivanovskii Inst. Virol., Moscow, USSR), K. V. Il'in, M. Ia. Volkova, A. F. Bykovskii and V. M. Zhdanov. *Dokl Akad Nauk SSSR* 215(4):976-979, 1974.

0326 PATHOMORPHOLOGY IN MAREK'S DISEASE IN CHICKS. (Rus.) Demkin, G. P. (Saratov Zoovet. Inst., USSR). *Veterinariia* (4):65-68, 1974.

0327 MORPHOGENESIS OF TYPE A ONCORNAVIRUSES IN DIVIDING CELLS. (Rus.) Zakhaleva, V. A. (N. F. Gamaleia Inst. Epidemiol. Microbiol., Moscow, USSR) and L. V. Gorokhova. *Vopr Virusol* (3):370-372, 1973.

0328 A COMPARATIVE STUDY OF THE ACTIVITY OF AN INHIBITOR OF HEPATIC CATALASE ISOLATED FROM VARIOUS TISSUES OF CC57BR MICE WITH MAZURENKO'S VIRAL LEUKEMIA. (Rus.) Koniukhov, A. F. (Sci. Res. Inst. Exp. Clin. Oncol., Moscow, USSR) and N. P. Mazurenko. *Probl Gematol Pereliv Krovi* 18(6):40-42, 1973.

0329 CYTOCHEMICAL CHARACTERISTICS OF LEUKEMIA CELLS FROM CC57BR MICE WITH ACUTE LEUKEMIA INDUCED BY MAZURENKO'S VIRUS. (Rus.) Peterson, I. S. (Inst. Pediatr., Moscow, USSR), M. D. Vialushkina and V. E. Gurtsevich. *Probl Gematol Pereliv Krovi* 18(6):38-40, 1973.

0330 ACTIVITY OF LIVER CATALASE IN MICE WITH LEUCOSES INDUCED BY MAZURENKO, FRIEND AND RAUSCHER VIRUSES. (Rus.) Konyukhov, A. F. (Acad. Med. Sci., Moscow, USSR) and N. P. Mazurenko. *Vopr Med Khim* 19(2):198-201, 1973.

0331 KARYOTYPIC FEATURES AND TRANSPLANTABILITY OF SOME CELL LINES IN MAMMALS. (Rus.) Stromskaya, T. P. (Acad. Med. Sci., Moscow, USSR) and A. A. Stavrovskaya. *Vopr Onkol* 20(2):60-67, 1974.

0332 FUCOSYLGLYCOLIPIDS IN CELLS TRANSFORMED BY A TEMPERATURE-SENSITIVE MUTANT OF MURINE SARCOMA VIRUS. (E.) Steiner, S. M. (Baylor Coll. Med., Houston, Tex.), J. L. Melnick, S. Kit and K. D. Somers. *Nature* 249(5450):682-684, 1974.

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0334 NO CROSSING OVER BETWEEN LINKED TUMOUR VIRUS LOCI IN THE HETEROGAMETIC SEX OF FOWL. (E.) Pani, P. K. (Houghton Poultry Res. Sta., Huntingdon, England). *Nature* 248(5449):592-594, 1974.

0335 ISOLATION OF PROTEINS BY GEL FILTRATION IN 6M GUANIDINIUM CHLORIDE: APPLICATION TO RNA TUMOR VIRUSES. (E.) Green, R. W. (Duke U. Med. Ctr., Durham, N.C.) and D. P. Bolognesi. *Anal Biochem* 57(1):108-117, 1974.

0336 BLOCKS IN GANGLIOSIDE SYNTHESIS IN TRANSFORMED HAMSTER CELLS AND THEIR REVERTANTS. (E.) Den, H. (Weizmann Inst. Sci., Rehovot, Israel), B.-A. Sela, S. Roseman and L. Sachs. *J Biol Chem* 249(2):659-661, 1974.

0337 INFECTIOUS C-TYPE VIRUS ISOLATED FROM A BABOON PLACENTA. (E.) Benveniste, R. E. (Natl. Cancer Inst., Bethesda, Md.), M. M. Lieber, D. M. Livingston, C. J. Sherr, G. J. Todaro and S. S. Kalter. *Nature* 248(5443):17-20, 1974.

- 0338 ADAPTATION AND INFECTION OF MOUSE BONE MARROW (JLS-V9) CELLS IN SUSPENSION CULTURE FOR PRODUCTION OF RAUSCHER LEUKEMIA VIRUS. (E.) Hodge, H. M. (Frederick Cancer Res. Ctr., Md.), F. Klein, A. K. Bandyopadhyay, O. R. Robinson, Jr. and G. P. Shibley. *Appl Microbiol* 27(1):224-231, 1974.
- 0339 TISSUE-CULTURAL AND MORPHOLOGICAL CHARACTERISTIC OF THE HERPES VIRUS TYPE "B" ISOLATED FROM CLINICALLY HEALTHY TURKEYS IN BULGARIA. (E.) Todorov, T. G. (Vet. Res. Inst. Immunol., Sofia, Bulgaria), R. S. Kasabov, V. Ivanov, S. Stoychev, B. H. Rezashki and Z. M. Mladenov. *Dokl Bolg Acad Nauk* 26(3):431-434, 1973.
- 0340 EFFECT OF cAMP ON NUCLEOSIDE METABOLISM. I. EFFECT ON THYMIDINE TRANSPORT AND INCORPORATION IN MONKEY CELLS (CV-1). (E.) Roller, B. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), K. Hirai and V. Defendi. *J Cell Physiol* 83(2):163-176, 1974.
- 0341 HUMAN ADENOID TISSUE AS SOURCE OF LYMPHOBLASTOID CELL CULTURE AND POSSIBLE RESERVOIR FOR HERPES-TYPE VIRUS. (E.) Ito, Y. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan), A. Ishimoto and T. Hosokawa. *Exp Hematol* 1(5):271, 1973.
- 0342 THE CHARACTERIZATION OF MURINE LEUKEMIA VIRUS IN HUMAN AND NON-HUMAN PRIMATE CELLS. (E.) Ablashi, D. V. (Natl. Cancer Inst., Bethesda, Md.), H. K. Oie, A. J. Dalton, G. R. Armstrong and U. Heine. *Exp Hematol* 1(5):304, 1973.
- 0343 EBV IN BURKITT'S LYMPHOMA AND OTHER HUMAN NEOPLASIAS. (E.) Gunven, P. (Karolinska Inst., Stockholm, Sweden), G. Klein, G. Henle, W. Henle, S. Singh and P. Clifford. *Exp Hematol* 1(5):304, 1973.
- 0344 KINETIC STUDY OF FRIEND LEUKEMIA. (E.) Smadja-Joffe, F. (Hosp. Paul-Brousse, Villejuif, France), C. Jasmin and E. Malaise. *Exp Hematol* 1(5):302, 1973.
- 0345 EFFECT OF RAUSCHER VIRAL LEUKEMIA ON THE F-FACTOR AND THE G₀ COMPARTMENT OF THE PLURIPOTENT HEMATOPOIETIC COLONY-FORMING UNIT. (E.) OKunewick, J. P. (Allegheny Gen. Hosp., Pittsburgh, Pa.) and E. L. Phillips. *Exp Hematol* 1(5):258, 1973.
- 0346 STEM CELL STUDIES (CFU-S AND CFU-C) AFTER RAUSCHER VIRUS INFECTION IN CBA MICE. (E.) Iturriza, R. G. (Dept. Clin. Physiol., U. Ulm, Germany) and H. J. Seidel. *Exp Hematol* 1(5):258-259, 1973.
- 0347 GROWTH PATTERNS *IN VITRO* OF RAUSCHER VIRUS INDUCED MURINE MYELOID LEUKAEMIAS. (E.) Bentvelzen, P. (Radiobiol. Inst., Bijswijk, The Netherlands), A. M. Aarssen, J. Brinkhof and G. J. Van Den Engh. *Exp Hematol* 1(5):253-254, 1973.
- 0348 REGRESSION OF PLANE WARTS FOLLOWING SPONTANEOUS INFLAMMATION. AN HISTOPATHOLOGICAL STUDY. (E.) Tagami, H. (Kyoto U. Sch. Med., Japan), A. Ogino, M. Takigawa, S. Imamura and S. Ofuji. *Br J Dermatol* 90(2):147-154, 1974.
- 0349 SPECIFIC MARKERS OF CHRONIC MYELOGENOUS LEUKEMIA (CML) CELLS (Ph, CHROMOSOME), THYMIC-DERIVED CELLS (TERMINAL TRANSFERASE), AND TYPE-C RNA TUMOR VIRUS (REVERSE TRANSCRIPTASE) IN BLASTIC LEUKEMIA. (E.) Gallo, R. (Bethesda, Md.), J. Bhattacharyya and P. Anderson. *J Clin Invest* 53(6):26a, 1974.
- 0350 VIRUS-INDUCED CELL FUSION ENHANCED BY PHYTOHEMAGGLUTININ. (E.) Reeve, P. (U. Coll. Hosp. Med. Sch., London, England), G. Hewlett, H. Watkins, D. J. Alexander and G. Poste. *Nature* 249(5455):355-356, 1974.
- 0351 COMPARATIVE STUDIES ON HSV TRANSFORMED AND HSV INFECTED L CELLS. (E.) Kraiselburd, E. N. (State U. New York, Buffalo). *Diss Abstr Int* 34(12):5818-B, 1974.
- 0352 EXPERIMENTAL HERPESVIRUS SAIMIRI AND ATELES LYMPHOMA AND LEUKEMIA IN NEW WORLD MONKEYS - MODELS FOR THE EPSTEIN-BARR VIRUS. (E.) Hunt, R. D. (Harvard Med. Sch., Southborough, Mass.) and L. V. Melendes. *Exp Hematol* 1(5):303, 1973.
- 0353 VIRUS SAIMIRI, A NON-HUMAN PRIMATE MODEL FOR HERPESVIRUS ASSOCIATED NEOPLASIA OF MAN. (E.) Ablashi, D. V. (Natl. Cancer Inst., Bethesda, Md.). *Exp Hematol* 1(5):303, 1973.
- 0354 SEPARATION AND ANALYSIS OF PROTEINS FROM FELINE LEUKEMIA VIRUS. (E.) Graves, D. C. (Michigan State U., East Lansing). *Diss Abstr Int* 34(12):6119-B - 6120-B, 1974.
- 0355 VIRUS-LIKE PARTICLES IN HUMAN LARYNGEAL PAPILLOMA. AN ULTRASTRUCTURAL STUDY. (E.) Ahmed, M. M. (Dept. Anat., U. Singapore) and D. K. Mukherjee. *Experientia* 30(4):361-363, 1974.
- 0356 AN IMPROVED QUANTITATIVE ASSAY FOR EPSTEIN-BARR (EB) VIRUS-INDUCED TRANSFORMATION OF LYMPHOCYTES. (E.) Robinson, J. (New Haven, Conn.), M. Newmuis, L. Heston and G. Miller. *J Clin Invest* 53(6):66a, 1974.

See also:

- * (Rev): 0012, 0013, 0017, 0024, 0028, 0029, 0030, 0033, 0037, 0038, 0039, 0048, 0057
- * (Chem): 0125
- * (Immun): 0360, 0362, 0370, 0374, 0377, 0381, 0385, 0395, 0397, 0399, 0401, 0423, 0430, 0436, 0437

- 0357 "COOPERATION" OF NORMAL AND MALIGNANT LYMPHOID CELLS IN THE IMMUNE RESPONSE AGAINST SHEEP ERYTHROCYTES. (E.) Boranic, M. (Lab. Exp. Therapy, Rudjer Boskovic Inst., Zagreb, Yugoslavia), I. Hrsak, T. Marotti, R. Mazuran and V. Silobrcic. *Biomedicine* 21(1):9-12, 1974.

Lymphoid leukemia cells from A/H mice were injected into lethally X-irradiated syngeneic mice, along with sheep red blood cells (SRBC - antigen) and normal thymocytes or bone marrow cells to determine whether they could participate in cellular interactions leading to the formation of antibody-forming cells (PFC). Few PFC were generated by leukemia cells given alone or mixed with bone marrow, but numerous PFC grew from the mixture of leukemia cells and thymocytes. Thus, the malignant lymphoid leukemia cells behaved as if they were a population of B-cells capable of cooperating with thymus cells. However, although this leukemia is not of T-type, there is no proof that it is of B-type. It is possible that the leukemia cells acquired the ability to lyse SRBC by having attached anti-SRBC antibodies produced by normal B-cell contaminating the inoculum. It is also possible that the leukemia cells were induced by the added T-cells into making their own antibodies against SRBC.

- 0358 BINDING OF AGGREGATED IgG BY LYMPHOCYTES IN CHRONIC LYMPHOCYTIC LEUKEMIA. (E.)

Augener, W. (Dept. Med., U. Essen, Germany), G. Cohnen and G. Brittinger. *Biomedicine* 21(1):6-8, 1974.

Blood lymphocytes from normal individuals and patients with chronic lymphocytic leukemia (CLL) were assayed for membrane-bound immunoglobulin (M-Ig), binding of aggregated IgG (Agg), and the formation of spontaneous rosettes with sheep red blood cells (SRBC). The majority of the lymphocytes from four of the five CLL patients exhibited M-Ig and Agg binding, but failed to form rosettes, indicating that these cells were of B cell origin. In the fifth patient, the majority of the blood lymphocytes were negative for M-Ig, bound Agg, and failed to form rosettes with SRBC; thus, these cells also appeared to be of B cell origin despite the absence of M-Ig. Most of the lymphocytes of the normal individuals exhibited no M-Ig, did not bind Agg, and formed rosettes with SRBC. These data suggest that M-Ig and the receptor for Agg are independent sites on the membranes of lymphocytes of B cell origin. Several membrane markers are necessary for the exact classification of lymphoid cells in lymphoproliferative disorders.

- 0359 IMMUNOGENICITY OF RAT HEPATOMA MEMBRANE FRACTIONS. (E.) Baldwin, R. W. (Cancer Campaign Labs., U. Nottingham, Great Britain), M. J. Embleton and M. Moore. *Br J Cancer* 28(5):389-399, 1973.

The cellular and humoral immune responses to sub-cellular fractions of hepatomas were analyzed using inbred Wistar rats and 4-dimethylaminoazobenzene

(DAB)-induced hepatomas. The principal expression of immunity elicited in syngeneic rats immunized with rat hepatoma membrane fractions was the development of a tumor specific antibody response. This antibody was demonstrable by membrane immunofluorescence staining of viable hepatoma cells in suspension; the sera exhibited complement dependent cytotoxicity for cultured hepatoma cells. In the absence of complement, however, the membrane immune sera protected the plated hepatoma cells from attack by sensitized lymph node cells. The cell mediated immune response elicited by hepatoma membrane immunization was weak as indicated by the colony inhibitory activity of lymph node cells from hepatoma cells *in vitro* and the adoptive transfer of immunity with peritoneal exudate cells. Correlated with this overall immune response pattern, membrane immunization did not elicit tumor rejection reactions. Membrane immunization, eliciting a prominent humoral immune reaction, conditioned the recipients so that they subsequently failed to elicit a tumor rejection immunity on treatment with irradiated tumor cells. These findings are relevant to current views that humoral factors operate antagonistically to limit cell mediated immunity to tumors.

- 0360 CHARACTERIZATION OF X/Gf MICE WITH RESPECT TO THEIR RESISTANCE TO ONCOGENESIS. (E.) Goldfeder, A. (Francis Delafield Hosp., New York, N.Y.). *Trans NY Acad Sci* 36(1):59-77, 1974.

A strain of mice designated X/Gf, inbred for the past 20 years by sister-brother matings, proved to have an extremely low susceptibility to the spontaneous development of neoplasms. Mice of this strain served as a model system in studies pertaining to the detection of endogenous characteristics that may be involved in resistance to neoplasia. The X/Gf mice produce high levels of antibodies against the mouse mammary tumor virus (MMTV), possess a high phagocytic activity and a high capacity to produce hemoantibodies, are resistant to polyoma virus, Friend leukemia virus (as adults), and to FBJ osteosarcoma virus, and exhibit low susceptibility to potent carcinogenic agents such as x-rays, urethan, 2-acetylaminofluorene, and 7,12-dimethylbenz(a)-anthracene. No variants from those noted in other inbred mice were found either in the capacity for interferon production or in a representative number of isozymes. The low susceptibility of X/Gf mice to neoplastic transformation is attributed to their efficient immunological surveillance.

- 0361 FACILITATION OF METASTASIS BY ANTITHYMOCYTE GLOBULIN. (E.) James, S. E. (Imperial Cancer Res. Fund, London, England) and A. J. Salsbury. *Cancer Res* 34(2):367-370, 1974.

Antithymocyte globulin increased the number, size, and rate of appearance of pulmonary metastases in female C57BL mice from implants of the syngeneic Lewis lung carcinoma without significantly increasing the weight of the primary tumor. To determine whether this effect was due to an earlier release of malignant cells from the primary tumor or to

facilitation of the subsequent implantation of the cells in the lungs, counts of the numbers of malignant cells in the blood of mice with Lewis lung carcinoma implants and experiments in which the primary tumor was excised at various times were conducted. These experiments indicated that antithymocyte globulin caused an earlier release of malignant cells into the circulation. Examination of the blood of control tumor-bearing mice showed a maximum level of immunoblasts 4 days after implantation of Lewis lung carcinoma, while treatment with antithymocyte globulin abrogated this response. These findings suggest that there is a possible correlation, in the antithymocyte-treated mice, between the absence of the immunoblast response and the earlier release of malignant cells from the primary tumor.

0362 COMPLEMENT-FIXING ANTIBODIES REACTIVE WITH EPSTEIN-BARR VIRUS IN SERA OF MARMOSETS AND PROSIMIANS. (E.) Gerber, P. (Bureau Biologics, FDA, Rockville, Md.) and D. Lorenz. *Proc Soc Exp Biol Med* 145(2):654-657, 1974.

Complement-fixing antibodies reactive with Epstein-Barr (EBV) antigens were demonstrated in significant titers in 23-64% of sera from imported and colony-born marmosets and prosimians. The specificity of the serologic reactions was demonstrated by absorption studies. Attempts to demonstrate EBV-reactive antibodies in marmosets or prosimian sera by indirect immunofluorescence tests using fluorescein-conjugated antisera to human or rhesus IgG were not successful. This may be due to the weak cross-reactivity of marmoset IgG with anti-IgG of higher primates detected by immunoelectrophoresis. These results indicate a widespread distribution of viruses antigenically related to EBV among the higher and lower nonhuman primates. It is thus suggested that these lower primates may be susceptible to experimental EBV infection and provide a model for the study of the pathogenicity of this virus.

0363 VIRUS-AUGMENTED TUMOR TRANSPLANTATION ANTIGENS: EVIDENCE FOR A HELPER ANTIGEN MECHANISM. (E.) Boone, C. W. (Natl. Cancer Inst., Bethesda, Md.), M. Paranjpe, T. Orme and R. Gillette. *Int J Cancer* 13(4):543-551, 1974.

While the homogenate of a transplantable simian virus 40 (SV40)-transformed fibrosarcoma of BALB/c mice was without tumor transplantation antigen (TTA) activity, a homogenate of the same tumor cells following infection with influenza virus or vesicular stomatitis virus retained TTA activity to a degree approaching that of whole cells. Ultraviolet inactivation of the virus in the homogenate did not affect its TTA activity. Strong evidence in favor of a helper antigen mechanism was provided by two findings: mice made tolerant to influenza virus could no longer be made tumor immune with the virus-infected tumor homogenate; and priming mice with three weekly injections of egg-grown influenza virus abrogated the ability of the virus-infected tumor homogenate to produce tumor immunity when it

was given during the fourth week. Although tumor-cell homogenates did not induce tumor immunity, they did elicit a delayed hypersensitivity (DH) reaction in the foot pad. It is hypothesized that the TTA on an intact tumor cell is made up of two components: a "DH-eliciting component" that survives homogenization of the cell but is not by itself immunogenic; and a native "helper component" which is required to make the DH-eliciting component immunogenic. This helper component is inactivated or destroyed by homogenization. The insertion of a virus protein into the plasma membrane near the TTA during virus replication introduces a substitute helper component which is not destroyed by cell disruption. The stability of this substitute helper component accounts for the persistence of TTA activity in the tumor homogenate.

0364 ABROGATION OF CELL-MEDIATED IMMUNITY BY HYPERIMMUNE ALLOANTISERUM: MECHANISMS AND CORRELATION WITH ALLOGRAFT ENHANCEMENT. (E.) Cohen, J. M. (Natl. Cancer Inst., Bethesda, Md.), S. S. Yang and L. W. Law. *Int J Cancer* 13(4):463-477, 1974.

Alloantiserum blocking of cell-mediated immunity as measured by a ^{51}Cr release cell-mediated cytotoxicity assay was characterized and correlated with the immunological enhancement of tumor allografts across H-2 barriers in B10.D2 mice. Alloantiserum blocking was immunologically specific, quantitative, and highly reproducible. Cytotoxicity could be blocked by adding alloantiserum directly to the reaction mixture or by pretreating the target cells with alloantiserum. Effector cells could also be specifically blocked by pretreatment with alloantigens or with a fraction isolated from a mixture of alloantiserum and ascitic fluid containing alloantibody. Pretreatment of the effector cells with alloantibody alone had no blocking effect. Upon purification, this fraction dissociated into IgG and a small molecular species with some biochemical and antigenic properties analogous to H-2 fragments. These observations indicate that the isolated fraction may have been an antigen-antibody complex consisting of alloantibody and H-2 alloantigen. In addition, blocking was surmountable under certain conditions by increasing the number of effector cells.

0365 ANTIBODIES TO AUTOLOGOUS TUMOR CELLS IN METHYLCHOLANTHRENE-INDUCED TUMORS IN MICE. (Rus.) Vetrova, E. P. (Inst. Problems Oncol., Kiev, USSR), M. I. Fedorovskaia, L. P. Kaminskaia and Iu. A. Umanski. *Vopr Onkol* 20(3):59-62, 1974.

Micro modifications of the cytotoxic and membrane fluorescence tests were used for detection of autologous antitumor antibodies in blood from BALB/c and C57Bl mice before and 1-4 months after a single injection of 1 mg methylcholanthrene in 0.1 ml peach oil. While tumors were developing, antitumor antibodies were detected in 7/8 of the BALB/c mice and 5/9 of the C57Bl mice by the cytotoxic test and in 2/3 of the BALB/c mice and 1/2 of

the C57Bl mice by the membrane fluorescence test. The higher frequency of humoral response in BALB/c mice may be due to less active absorption of antibody on the surface of tumor cells, resulting in higher titers in the blood. Periodic increases and decreases in the cytotoxic index occurred in 69% of BALB/c mice and in 92.3% of C57Bl mice.

0366 HETEROORGANIC ANTIGENS OF HUMAN GASTRIC CANCER. (Rus.) Avdeev, G. I. (P. A. Gertsen Sci. Res. Inst. Oncol., Moscow, USSR). *Vopr Onkol* 22(2):36-40, 1974.

Hyperimmune rabbit serum was prepared by giving rabbits three cycles of injections with extracts from a gastric adenocarcinoma. After concentrating the serum with ammonium sulfate, antibodies were neutralized by adding alcohol precipitates from pooled human serum and extracts from normal human gastric mucosa. In the gel precipitation reaction this hyperimmune serum formed 1-2 lines with extracts from human stomach tumors but not with extracts from normal gastric mucosa. Positive reactions occurred between the serum and extracts from 10 of the 11 human stomach tumors and with only 2 of 14 samples of normal gastric mucosa. Positive gel precipitation reactions also occurred between the serum and extracts from a sigmoid carcinoma, one of two pulmonary carcinomas and extracts from normal lungs, spleen and thyroid. When normal lung extract was added to the agar along with hyperimmune serum, no reaction occurred with pulmonary antigens and the reaction with stomach cancer antigens became less intense. Although hyperimmune serum had reacted with 5 of the 7 stomach cancer antigens, reactions occurred with only 3 after neutralization. Neutralized hyperimmune serum continued to react with extracts from normal kidney and small intestine. These findings and literature data suggest that stomach cancer extracts contain antigens which are not present in the normal stomach but do occur in other normal human organs. These appear to include one antigen found in the kidneys; a second antigen present in the spleen and lung; and a third which is found in the spleen, lung and thyroid.

0367 FAILURE OF SHIER'S CHEMICAL VACCINE TO PROTECT BALB/c MICE AGAINST TRANSPLANT AND CHEMICALLY INDUCED TUMORS. (E.) Cook, M. M. (Merck Inst. Therapeutic Res., West Point, Pa.), A. F. Wagner, V. M. Larson, A. A. Tytell, T. Y. Shen and M. R. Hilleman. *Proc Soc Exp Biol Med* 145(2):636-640, 1974.

The di-N-acetylchitobiosyl poly(L-asparagine) was prepared and administered to groups of 24 male and female BALB/c mice. In the transplant challenge section of the study 6 mice which had received the antigen were given 10^5 , 5×10^5 , 10^6 , or 10^7 XS63.5 myeloma transplant tumors at any challenge dose level used. The average time period for tumor occurrence was the same in the vaccine and in control animals. In the chemical challenge experiments, 0.1 ml (0.5 mg) 3-methylcholanthrene

was inoculated i.m. There was no significant suppression in the tumor incidence or delay in time of tumor occurrence in the groups immunized with the vaccine as compared to controls. Thus the chemical vaccine containing di-N-acetylchitobiosyl poly(L-asparagine) was shown ineffective in preventing XS63.5 myeloma transplant tumors and 3-methylcholanthrene-induced tumors in BALB/c mice.

0368 STIMULATION OF MURINE LYMPHOCYTES BY A SYNGENEIC, METHYLCHOLANTHRENE-INDUCED MAMMARY CARCINOMA. (E.) Colgrove, G. S. (Radiobiol. Lab., U. California, Davis) and M. Shifrine. *Proc Soc Exp Biol Med* 145(4):1317-1320, 1974.

A mixed lymphocyte-tumor reaction was used to study the antigenicity of a methylcholanthrene-induced mammary carcinoma. Spleen cells were obtained from female BALB/c mice which had not been treated with tumor cells previously. Mitomycin C-treated tumor cells stimulated the syngeneic spleen cells to incorporate increased amounts of ^{14}C -thymidine. Stimulation indices varied from 2.35 to 3.10, a marginal level. These results reflect the antigenic difference between normal and neoplastic cells in a methylcholanthrene-induced mammary carcinoma system. It was concluded that the tumor under study was of relatively low antigenicity.

0369 PREFERENTIAL EFFECTIVENESS OF IMMUNE COMPLEXES IN THE ENHANCEMENT OF TUMOR ALLOGRAFTS. (Fr.) Duc, H. T. (St. Antoine Hosp., Paris, France), R. G. Kinsky and G. A. Voisin. *Ann Immunol (Inst Pasteur)* 124C(4):567-572, 1973.

A spontaneous sarcoma (SaI) from A/Jax mice was injected i.p. into male and female IC mice and male CBA mice to study the effect of transplantation antigens and antibodies on the growth of these allografts. Antigen was obtained from the supernatant of sarcoma SaI ascites cells after incubation for 3 hr in buffered (pH 7.4) physiological saline. Antigen-antibody complexes were then prepared by mixing antigen with specific antiserum and were tested *in vivo*. Lethal tumors which developed in control male IC mice were significantly smaller in diameter and survival times were significantly longer than in mice injected with the antigen-antibody complex or with an excess of antibody. In contrast, the survival times of the control mice were shorter than those of mice injected with an excess of antigen in highly diluted immune serum. Addition of immune serum to isogeneic material from spleen cells of IC mice conferred significant protection, particularly when the serum was administered in the largest dose tested (1:80 dilution). Since female IC mice are almost completely resistant to the tumor used, only a slight enhancing effect was obtained when females were pretreated with an antigen-antibody complex containing an excess of antibodies. In male CBA mice, which are much more resistant to sarcoma SaI than are male IC mice, pretreatment with soluble antigen (obtained with the use of

potassium cholate) and an equivalent quantity or excess of antibodies gave results similar to those obtained with IC mice under the same conditions. These results demonstrated that small quantities of antibodies, which are almost completely inactive when administered alone, can acquire enhancing properties when they are administered after reaction with the corresponding antigen. The antigen had little or no activity in the absence of antibodies. The results suggest that antigen-antibody complex acts directly on reactive lymphoid cells.

0370 A COMPARISON OF MEMBRANE PROTEINS OF NORMAL AND TRANSFORMED CELLS BY LACTO-PEROXIDASE LABELING. (E.) Hogg, N. M. (Dept. Zool., U. College, London, England). *Proc Natl Acad Sci USA* 71(2):489-492, 1974.

The enzyme lactoperoxidase was used to iodinate (^{125}I) accessible proteins on the membranes of intact virally transformed (derived from the murine 3T3 line A31) and untransformed (BALB/c 3T3, Swiss 3T6, and secondary cultures of mouse embryo fibroblasts (TO)) cells. The lactoperoxidase labeling patterns of all of the untransformed cells were identical. The patterns of the transformed cells were essentially similar to the normal cells, except that a heavily labeled band (L1) with a molecular weight of approximately 250,000 daltons which was found in all untransformed cells was absent from the transformed cells. The data indicated that the lactoperoxidase was labeling only the proteins exposed externally on the cell membrane. When Coomassie-blue-stained membrane preparations were compared, a band was seen in the normal cells which comigrated with the lactoperoxidase-labeled band. In the transformed cell membranes, three discrete bands were present in the same position. Again, the major differences between the membrane proteins of the normal and transformed cells were found in the L1 region. Thus, the expression of this protein may be altered when cells are in the transformed state.

0371 PREFERENTIAL CUTANEOUS INFILTRATION BY NEOPLASTIC THYMUS-DERIVED LYMPHOCYTES: MORPHOLOGIC AND FUNCTIONAL STUDIES. (E.) Edelson, R. L. (Natl. Cancer Inst., Bethesda, Md.), C. H. Kirkpatrick, E. M. Shevach, P. S. Schein, R. W. Smith, I. Green and M. Lutzner. *Ann Intern Med* 80(6):685-692, 1974.

The abnormal lymphocytes from three patients with mycosis fungoides and four patients with lymphocytic leukemia accompanied by exfoliative erythroderma had membrane properties of thymus-derived lymphocytes (T cells). Three of the lymphocytic leukemia patients were diagnosed as having Sezary syndrome. The abnormal circulating cells of the fourth patient differed morphologically from those of the classical Sezary syndrome and its "small cell variant" and had receptors characteristic of both bone marrow (B) derived cells and T cells. The T cells from two of the lymphocytic leukemia patients were essentially unresponsive

to mitogens, and one patient's lymphocytes failed to stimulate allogeneic normal lymphocytes in mixed leukocyte cultures, despite the presence of histocompatibility antigens. The abnormal circulating T cells in each of the leukemic patients not only preferentially infiltrated the skin but spared the bone marrow. Each of the mycosis fungoides patients showed generalized cutaneous plaques which were densely infiltrated by numerous abnormal lymphoreticular cells. The data suggest that lymphoproliferative disorders with widespread cutaneous infiltration are frequently T-cell malignancies with several distinguishing features. The data further indicate that both Sezary syndrome and mycosis fungoides are T-cell malignancies.

0372 INHIBITION OF NORMAL LYMPHOCYTE TRANSFORMATION BY PLASMA AND LYMPHOCYTE FACTORS IN CHRONIC LYMPHATIC LEUKAEMIA. (E.) Tavadia, H. B. (U. Dept. Path., Glasgow Royal Infirmary, Scotland), R. B. Goudie and W. D. Nicoll. *Clin Exp Immunol* 16(2):177-182, 1974.

The plasma of apparently healthy untreated patients with chronic lymphatic leukemia (CLL) was examined for inhibitors of normal lymphocyte transformation. The phytohemagglutinin transformation of normal lymphocytes was significantly inhibited by the plasma and lymphocyte extracts of six of the eight CLL patients compared with similar material from matched controls. Heating of the plasma and lymphocyte extract from four CLL cases at 55°C for 60 minutes resulted in significant and probably complete abolition of the inhibitory activity. There was no significant difference in the viability of normal lymphocytes cultured in the plasma or lymphocyte extracts of the CLL patients compared with those from the normal controls. Since the concentration of inhibitor in the lymphocytes was much greater than in the plasma and both inhibitors were thermolabile, the plasma inhibitor may have been produced by the leukemic cells. These data indicate modifications of normal T-cell function by constituents of neoplastic lymphocytes, although the effect may be due to an exaggeration of a normal mechanism by which the surface properties of T cells are modified by products of B cells.

0373 THE INDUCTION OF TUMOUR IMMUNITY IN MICE USING GLUTARALDEHYDE-TREATED TUMOUR CELLS. (E.) Sanderson, C. J. (Div. Surg. Sci., Clin. Res. Ctr., Harrow, Great Britain) and P. Frost. *Nature* 248(5450):690-691, 1974.

Glutaraldehyde-treated methylcholanthrene-induced BALB/c tumor cells (5×10^7) were inoculated i.p. into BALB/c female mice. After 2 weeks these mice and a group of nontreated controls were challenged i.p. with live tumor cells. The nonimmunized control mice challenged with 10^5 tumor cells survived for about 20 days, while the immunized mice were completely protected against this challenge. The immunized mice were not protected against challenge by 10^6 tumor cells, and mice immunized with the same number of irradi-

ated cells showed less protection. Mice left for 27 days between immunization and challenge showed only partial protection. Glutaraldehyde-treated cells stored for 2 weeks at 4°C offered full protection. Preliminary data with a spontaneously arising mammary tumor corroborated these findings, and indicated that protection against a higher challenge dose can be achieved with multiple immunization. Mice treated with a similar number of glutaraldehyde-treated syngeneic spleen cells showed no protection. The glutaraldehyde may preserve the tumor antigenicity or the chemical modification of the proteins may produce and enhanced cellular immunity at the expense of the humoral response.

- 0374 EPSTEIN-BARR VIRUS-ASSOCIATED MEMBRANE-REACTIVE ANTIBODIES DURING LONG TERM SURVIVAL AFTER BURKITT'S LYMPHOMA. (E.) Gunven, P. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), G. Klein, P. Clifford and S. Singh. *Proc Natl Acad Sci USA* 71(4):1422-1426, 1974.

The antibodies to Epstein-Barr virus (EBV) associated cell membrane antigens (MA) were studied in Burkitt's lymphoma (BL) patients who had survived more than 2 years with or without recurrences. The antibodies to MA persisted or slowly decreased during the prolonged uncomplicated survival of BL patients in remission. Immune stimulant treatment with BCG (Bacille Calmette Guérin vaccine) markedly increased the antibody titers in clinically tumor-free patients, as did triple vaccine. Four patients had recurrences more than 1 year after hospital admission; these recurrences were preceded by a tumor regression period of more than 6 months. Four of these patients showed significantly decreased antibody titers starting 4 to 8 months prior to the detection of the recurrences and lasting until after their recognition; in the fourth patient, the antibody titers increased during the 2 years before relapse.

- 0375 MODULATION OF CELL-SURFACE ANTIGENS OF A MURINE NEUROBLASTOMA. (E.) Akeson, R. (UCLA Sch. Med., Los Angeles, Ca.) and H. R. Herschman. *Proc Natl Acad Sci USA* 71(1):187-191, 1974.

Rabbit antisera to morphologically differentiated (i.e., serum-free, process-bearing) cells derived from clone N18 of the C1300 murine neuroblastoma were assayed by complement fixation against the particulate fraction from N18 cells maintained on medium without serum (N18-SF, differentiated) and the particulate fractions of N18 cells grown in suspension culture (N18-sus, undifferentiated, nonprocess bearing). N18-sus fixed less complement than did N18-SF. Adsorption of the antisera with the undifferentiated cells removed the reactivity to cells without processes, while the reactivity with the serum-free cells which possessed processes was retained. Indirect immunofluorescence studies confirmed the results obtained by complement fixation and indicated that antibodies to the surface antigens of the process-bearing

cells could be adsorbed by particulate preparations from brain, but not liver, spleen, or kidney. Thus, morphological differentiation of murine neuroblastoma cells induced by maintenance in serum-free medium results in antigenic alterations in the cell membranes, and brain particulate preparations contain antigens that can react with and remove antibodies directed to the antigens found on morphologically differentiated cells, while similar amounts of other organ preparations are unable to absorb such antibodies.

- 0376 TUMOR RESISTANCE OF MICE INFECTED WITH *SALMONELLA ENTERITIDIS* 11RX. THE ROLE OF PERITONEAL EXUDATE CELLS. (E.) Ashley, M. P. (Dept. Microbiol., U. Adelaide, Australia) and D. Hardy. *Aust J Exp Biol Med Sci* 51(6):801-809, 1973.

(C57BL X Balb/c) F_1 hybrid mice were injected i.p. with 10^6 *Salmonella enteritidis* 11RX (11RX); 18 days later these and nontreated control mice were injected i.p. with 10^6 Ehrlich ascites tumor (EAT) cells. While there was progressive tumor growth in the control mice, there was a rapid fall in the number of EAT tumor cells recovered from the peritoneal cavity of the carrier mice. In a second experiment, carrier mice given 10^5 11RX 11 or 17 days previously, and normal control mice were injected i.p. with 10^6 ^{51}Cr -labeled EAT cells. The removal of cells associated with ^{51}Cr was more rapid in the 11RX carrier mice than in the control mice. In a third experiment, normal mice were injected i.p. with 10^6 ^{51}Cr -labeled EAT cells mixed with 2×10^7 peritoneal exudate cells (PEC) or splenic leucocytes from carrier mice given 10^5 11RX i.p. 12 days earlier. The increased i.p. clearance of EAT associated with ^{51}Cr was partially transferable with PEC but not with splenic leucocytes from 11RX carrier mice. In a fourth experiment, ^{51}Cr -labeled EAT cells were incubated *in vitro* for up to 25 hours with PEC and spleen cells from carrier mice and PEC from normal mice. While there was some tumor cell lysis in the presence of normal PEC, the cytolytic effect of PEC from 11RX carrier mice was much greater. These results indicate that the 11RX carrier mice possessed an anti-tumor mechanism at the time of tumor challenge and that the effect was probably not due to a primary immune response to the EAT.

- 0377 HUMORAL AND CELLULAR IMMUNE RESPONSES IN SUSCEPTIBLE AND RESISTANT STRAINS OF MICE INFECTED WITH FRIEND LEUKEMIA VIRUS. (E.) Ceglowski, W. S. (Dept. Microbiol., Pennsylvania St. U., University Park), B. P. Campbell, R. F. Mortensen and H. Friedman. *Proc Soc Exp Biol Med* 146(2):619-624, 1974.

Young adult Balb/C (highly susceptible to Friend leukemia virus (FLV) infection) and C57BL/6 (resistant to FLV infection) mice were inoculated i.p. with a highly infective strain of FLV and their humoral and cell-mediated immune responses determined. The infected Balb/C mice showed a prompt and prolonged depression of antibody responsiveness

to sheep erythrocytes (assessed at the level of individual antibody forming cells and serum hemolysins), as well as marked impairment of cellular immunity to mycobacterial antigens (assessed at the level of cell-mediated immunity using a macrophage migration inhibition assay). In contrast, the infected C57Bl/6 mice showed a transient but significant depression of antibody formation to sheep erythrocytes but no depression of cell-mediated immunity to the mycobacteria. FLV in high titer could be recovered from the spleen, serum, and other organs of the C57Bl mice at least 5-7 days after infection, indicating that the virus was replicating in these animals without inducing any signs of disease or pathology. The presence of virus was correlated with the transient depression of immune responsiveness, supporting the view that virus replication and immunosuppression are concomitant events and probably related. The data appear to reflect the relative importance of cell-mediated versus humoral immunity in resistance to leukemia virus induced leukemogenesis.

0378 EFFECTS OF CYCLOPHOSPHAMIDE ON IMMUNITY AGAINST CHEMICALLY-INDUCED SYNGENEIC MURINE SARCOMAS. (E.) Steele, G. (Dept. Surg., Denver Gen. Hosp., Colo.) and G. E. Pierce. *Int J Cancer* 13(4):572-578, 1974.

The effects of cyclophosphamide (CY) on tumor immunity against syngeneic murine fibrosarcomas induced by 3-methylcholanthrene (3-MCA) were studied using transplantation techniques. Five groups of female BALB/c mice were challenged with viable 3-MCA-induced sarcoma cells (AT-008). Mice bearing a sensitizing transplant of this tumor at the time of challenge were significantly resistant to challenge tumor growth compared with nonsensitized, untreated (with CY) controls and nonsensitized mice pretreated with CY. Animals which had been sensitized by inoculation and subsequent excision of this tumor were more resistant than the tumor-bearing mice. The greatest resistance, however, was seen in animals bearing syngeneic transplants of AT-008 and treated with CY 6 days prior to challenge. These findings suggest that CY not only fails to suppress but may actually intensify established tumor immunity in this animal system. Thus, tumor growth inhibition achieved with some chemotherapeutic agents may be accomplished partially via immunologic mechanisms.

0379 IMMUNOSUPPRESSIVE AND IMMUNOSTIMULATORY FACTORS PRODUCED BY MALIGNANT CELLS IN VITRO. (E.) Wong, A. (Dept. Path., Queen's U., Kingston, Ontario, Canada), R. Mankovitz and J. C. Kennedy. *Int J Cancer* 13(4):530-542, 1974.

The addition of small numbers of irradiated mouse fibrosarcoma cells to cultures containing syngeneic mouse spleen cells and sheep erythrocytes resulted in almost complete inhibition of the expected anti-sheep hemolytic plaque-forming cell responses; the addition of even smaller numbers resulted in stimulation rather than inhibition. This same pattern was reproduced when various other types of

syngeneic and allogeneic malignant cells were tested under similar conditions. The presence of strong (H-2) histocompatibility differences had no apparent effect. Metabolically active irradiated malignant cells were required to produce inhibition; dying cells or soluble extracts of cells were ineffective. However, serum-free supernatants from healthy cultures of nonirradiated fibrosarcoma cells were inhibitory at high concentrations and stimulatory at low concentrations, in a pattern similar to that observed when intact irradiated fibrosarcoma cells were used. High-speed centrifugation of such supernatants sedimented the stimulatory material but left the inhibitory material in solution. When syngeneic fetal fibroblasts were substituted for the fibrosarcoma cells, the stimulatory material could be sedimented by high-speed centrifugation. However, very little inhibitory effect was produced by either intact fibroblasts or their culture supernatants, except when unusually high concentrations were used. Thus, at least some types of healthy malignant cells release soluble material capable of inhibiting immune responses; their nonmalignant counterparts produce little if any inhibitor.

0380 SILENT MATERNAL TRANSMISSION OF AUSTRALIA ANTIGEN. (E.) Mazzur, S. (Inst. Cancer Res., Philadelphia, Pa.), B. S. Blumberg and J. S. Friedlaender. *Nature* 247(5435):41-43, 1974.

Immunological subtyping was used to discover any existing relation between Australia antigen carried by different members of the same family. The sera were collected in 18 villages in south central Bougainville and represent 85% of the healthy residents over 2 yr of age. There was an Au carrier rate of 10.2%. Family clustering was noted and of 32 families tested, there were 11 in which 2 different combinations of antigens were segregating. Asymptomatic carriers living in the same household could have different subtypes of Australia antigen, thus ruling out household infection or maternal transmission as the only explanation for the observed family clustering. However, in families where the mother was an asymptomatic carrier, the 22 children who were carriers, with a single exception, had the same subtype as their mother. Among 12 families where the mother was positive, 1 had mixed subtypes while among the 20 families in which the mother did not have Au, 10 families had antigen of different subtypes, which reflected the subtypes in the general population of the village. Among 6 families in which the father was positive, 4 had mixed subtypes. Thus it is demonstrated that vertical transmission from asymptomatic mothers to their asymptomatic children occurs in this environment. Segregation analysis of the distribution of Au in these sera revealed the segregation pattern expected of autosomal recessive inheritance. Women who become Au carriers by virtue of genetic susceptibility can be expected to transmit the antigen to some of their children whether or not the children are homozygous for the postulated recessive Au susceptibility gene. Thus a new maternal transmission line can be established from a genetically susceptible

woman whose own mother was not a carrier if the susceptible woman is exposed to infection.

- 0381 T LYMPHOCYTE REQUIREMENT FOR MSV TUMOUR PREVENTION OR REGRESSION. (E.) Collavo, D. (Inst. Pathol. Anat., U. Padova, Italy), A. Colombatti, L. Chieco-Bianchi and A. J. S. Davies. *Nature* 249(5453):169-170, 1974.

Both male and female CBA mice were thymectomized at 2 months of age. Irradiation with 850 rad commenced 2 weeks later and i.v. injection with 5×10^6 syngeneic bone marrow cells was completed so as to render the mice deprived for T cell functions. A cell-free tumor extract of M-MSV (murine sarcoma virus Moloney isolate) was injected i.m. (0.05 ml of the extract diluted to 10^{-2} g equivalent). Of 30 deprived mice, 27 developed tumors with a latent period of 17 days. Of these 27, 24 died with progressive tumors 2-3 months following M-MSV injection. No tumors occurred in the M-MSV-injected controls. Thus the deficiency of T cell population was responsible for the induction and progression of tumors in the deprived mice. Deprived mice were grafted with neonatal thymus lobes at various times before and after M-MSV injection. Mice receiving the graft 1, 5, or 25 days after injection presented a tumor incidence of 87.5, 69, and 100%, resp. Mice grafted 5 days following injection presented 100% regression, while those grafted 25 days after injection presented tumors which progressed till death of the host. The time needed for regression was greater (31 days) for mice grafted on the 5th day than that needed for mice grafted on the first day following injection (13 days). Both deprived and reconstituted mice produced virus-neutralizing antibody in free form.

- 0382 THE DETECTION OF AN ANTIGEN PRESENT IN GASTRIC CARCINOMA. (E.) Hocking, W. (Dept. Med., Tulane U. Sch. Med., New Orleans, La.), A. C. Epps and K. Akdamar. *Dig Dis* 19(6): 537-546, 1974.

Counterimmunoelectrophoresis was used to detect antigenic sulfoglycoproteins in 36 human gastric aspirations and indirect immunofluorescence was used to detect them in 32 gastric biopsies. Patients with gastric carcinomas, lymphomas and benign gastric lesions were studied, along with patients with no evidence of gastric disease. Specific antisera to sulfoglycoproteins found in the aspirates of the gastric carcinoma patients were produced in rabbits and later absorbed to increase specificity. Fluorescent staining was observed in the tissues of the gastric carcinoma patients, a more diffuse fluorescent staining being noted in the biopsies from the patients with normal gastric mucosa and other forms of gastric pathology. Counterimmunoelectrophoresis demonstrated a single precipitin band in all aspirates from the gastric carcinoma patients, in one lymphoma patient, and in one patient with gastric polyps showing atypical hyperplasia. The remaining aspirates showed no precipitin bands. Counter-

immunoelectrophoresis appears to have greater diagnostic value for the detection of gastric sulfoglycoproteins than the indirect immunofluorescent technique, indicating that the former may prove useful in the diagnosis of gastric carcinoma.

- 0383 AN EXAMINATION OF THE POSSIBLE INTER-RELATIONSHIPS BETWEEN SERUM CONCENTRATIONS OF CARCINOEMBRYONIC ANTIGEN AND OTHER GLYCOPROTEINS. (E.) Payne, M. (Dept. Clinical Chem., U. Birmingham, Great Britain), J. Leonard, J. King, S. N. Booth and P. W. Dykes. *Ann Immunol (Inst Pasteur)* 124C(4):633-634, 1973.

Sera from patients with cancer or chronic inflammatory diseases were analyzed for their concentrations of carcinoembryonic antigen (CEA), α_1 -antitrypsin, α_1 -acid glycoprotein, haptoglobin, ceruloplasmin, transferrin, IgA, and IgG. There was a positive correlation at the 0.01 level between CEA and α_1 -acid glycoprotein and α_1 -antitrypsin, and at the 0.05 level with total serum mucoids, ceruloplasmin, and haptoglobin. However, it appeared that these correlations arose from the existence of elevated CEA values in a small random group of patients with high serum glycoprotein concentrations, there being no greater tendency for CEA elevation at very high versus marginally high glycoprotein levels. Thus, CEA measurements do not appear to be influenced by the serum concentrations of any of the other serum proteins measured, and it is therefore likely that the CEA measurements are specific.

- 0384 THE ASSOCIATION OF ILLNESSES WITH ABNORMAL IMMUNOLOGIC FEATURES WITH IRRADIATION OF THE THYMIC GLAND IN INFANCY: A PRELIMINARY REPORT. (E.) Hempelmann, L. H. (U. Rochester, Sch. Med. Dentistry, N.Y.) and J. Grossman. *Radiat Res* 58(1):122-127, 1974.

The incidence of surgically removed neoplasms and other diseases among 2872 persons who had been treated with X-rays in infancy for alleged thymic enlargement was compared with that among 5055 untreated siblings; the study was conducted via mail survey. The results indicated that the incidence of asthma was higher among the treated subjects than the untreated siblings, as was the incidence of rare illnesses (collagen disease, blood dyscrasias, lymphoreticular disease, gastrointestinal disease, neuromuscular disease, and thyroid disease) with abnormal immunological features. Immunologic tests carried out on 105 of the irradiated subjects and 50 of the untreated siblings showed no significant differences in the immunologic responses of the two groups. The 3-fold excess of rare diseases among the irradiated subjects may have resulted from radiation damage to the infant thymus glands.

- 0385 CELL SURFACE ANTIGENS ASSOCIATED WITH MURINE LEUKEMIA VIRUS: DEFINITION OF THE G_L AND G_T ANTIGENIC SYSTEMS. (E.) Nowinski, R. C. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and E. D. Peters. *J Virol* 12(5):1104-1117, 1973.

Two new serological specificities were identified on the surface of murine leukemia virus (MuLV)-infected cells by direct and absorption immunofluorescence tests. Both antigens were detected with antisera prepared in rats that were growing transplants of syngenic MuLV-induced leukemias. Antigen G_L was defined with the AKR leukemia K36 as the test cell; antigen G_T was defined with the W/Fu leukemia C58(NT)D as the test cell. G_L and G_T antigens were serologically and genetically independent of the MuLV-induced Gross and G_{LX} cell-surface antigens. G_L and G_T antigens were found in normal lymphoid cells of mice from high-leukemic strains, but not in lymphoid tissues of mice from most low-leukemic strains. Tumors and leukemias of mice of low-leukemic strains often were G_L and G_T positive. Similarly, infection of normal cells with MuLV resulted in expression of G_L and G_T . With ferritin-labeled antibody the G_L and G_T antigens were observed on virus-free segments of the cell surface. Genetically, G_L and G_T antigens were each controlled by two dominant unlinked genes in AKR mice; these same antigens were each controlled by three or more unlinked genes in C58 mice. Penetration of G_L and G_T regulatory genes was dependent upon the FV-1 genotype of the host. Expression of G_L antigen was closely associated with virus production, whereas expression of G_T antigen was less closely associated.

0386 CHANGES IN BACK-TRANSPLANTABILITY BY FLUID-SUSPENSION CULTURE AND BY LONG-TERM OF CULTIVATION OF TWO TISSUE CULTURE CELL STRAINS, JTC-1 AND JTC-2, ORIGINATED FROM RAT ASCITES HEPATOMA AH-130. (E.) Katsuta, H. (Inst. Med. Sci., U. Tokyo, Japan), T. Takaoka, K. Ito and H. Okumura. *Japan J Exp Med* 43(6):483-493, 1973.

Two cell strains, JTC-1 and JTC-2, which were derived from the rat ascites hepatoma AH-130, showed decreased back-transplantability to animals when transferred to fluid-suspension culture, rotated at the speed of 3,000 rotations per hour. The results of experiments repeated 5 times revealed similar findings. The cells cultivated in fluid-suspension culture exhibited a higher rate of oxygen consumption and a lower rate of glucose uptake than in static culture. These changes markedly varied with culture stage in fluid-suspension culture but not in static culture. Prolonged cultivation of the strains in static culture also resulted in marked loss of back-transplantability in JTC-2. Shift in chromosome number of hypodiploidy was observed in both cases. It is not clear, however, whether this shift was closely related to the decrease in back-transplantability.

0387 THE PROLIFERATIVE RESPONSE OF T LYMPHOCYTES TO ALLOANTIGENS IN IRRADIATED MICE: A MIXED LYMPHOCYTE REACTION *IN VIVO*. (E.) Sprent, J. (Basel Inst. Immunol., Switzerland). *Transplant Proc* 5(4):1725-1729, 1973.

When CBA/J(H-2^k) T cells were injected into heavily irradiated (CBA/J X C57BL/6 (H-2^b) F₁ hybrid mice, the cells moved predominantly to the spleen and

lymph nodes and there responded against the allo-antigens of the host by blast transformation and proliferation; no evidence of cell proliferation was found in irradiated F₁ recipients of F₁ T cells. The extent of cell proliferation in the spleen and lymph nodes can be quantitated by measuring the uptake of ³H-thymidine after its i.v. injection. This method has indicated that parental thoracic duct lymphocytes, mesenteric lymph node cells, and thymus cells proliferate extensively in irradiated F₁ mice. A similar method for estimating lymphocyte proliferation in irradiated allogeneic mice involves injecting 5-iodo-2'-deoxyuridine-¹²⁵I i.p. then measuring radioactivity in the spleen 1 day later. Most of the cells that proliferate after injection into irradiated F₁ mice appear to be T cells, although B cells may also proliferate in response to alloantigens *in vivo*. The main immunogenic stimulus in the thymus-dependent areas of irradiated semi-allogeneic mice is probably not provided by the host T cells; a variety of cell types can stimulate allogeneic lymphocytes, cells of bone marrow origin being particularly effective. The immunogenic stimulus appears to be provided by antigen released from the cells following degradation by macrophages.

0388 INFLUENCE OF IMMUNOSUPPRESSION ON THE GROWTH OF TRANSPLANTS OF SPONTANEOUS MAMMARY TUMOURS IN MICE. (E.) Gruntenko, E. V. (Inst. Cytol. Genet., Siberian Branch, Acad. Sci. USSR, Novosibirsk). *Folia Biol (Praha)* 19(6):414-419, 1973.

The growth of syngeneic mammary tumors transplanted to mice infected with the mammary tumor virus was suppressed by thymectomy at 6 days of age, injection of cyclophosphamide, 300R total-body irradiation, administration of antilymphocyte serum, thymectomy of adults with subsequent 750R irradiation and administration of syngeneic bone marrow cells. Thymectomy of adult mice with subsequent 750R irradiation and administration of syngeneic bone marrow cells did not suppress the growth of a syngeneic hepatoma induced by a chemical carcinogen. Thymectomy at 6 days of age stimulated the growth of mammary tumors in virus-free (C57BL x C3H)F₁ mice. Evidence supports the suggestion that the growth of mammary tumor transplants is immunologically enhanced in virus-infected mice.

0389 CONCOMITANT IMMUNITY TO SYNGENEIC METHYLCHOLANTHRENE-INDUCED TUMOURS IN MICE. OCCURRENCE AND SPECIFICITY OF CONCOMITANT IMMUNITY. (E.) Kearney, R. (Dept. Bacteriol., U. Sydney, Australia) and D. S. Nelson. *Aust J Exp Biol Med Sci* 51(6):723-735, 1973.

Sarcomas which had been induced in male CBA/J and female A/J mice by 3-methylcholanthrene injections were minced and suspended in Waymouth's medium. 10⁷ tumor cells were then injected s.c. into the flanks of mice, and at various intervals thereafter the tumor-bearing mice and mice which had not received primary isografts were challenged with 10⁶ viable cells injected s.c. into a hind

footpad. The mice bearing the progressively growing isografts resisted the growth of cells of the same tumor injected into the footpad. Resistance was manifested in two phases: in the first, resistance was specific for the original tumor; in the second, the mice were resistant to other lines of syngeneic methylcholanthrene-induced tumors. Mice from which the first tumor was completely excised during the development of the first phase had lost their resistance when challenged 5 days later. Mice from which the tumors had been incompletely excised were as resistant as mice with intact tumors. The injection of tumor cells into the footpads of normal mice was followed by swelling of the feet, the degree of which served as an index of tumor growth. The resistance of tumor-bearing mice to footpad isografts of tumors is an example of concomitant immunity.

0390 SKIN TUMOURS IN IMMUNOSUPPRESSED PATIENTS. (E.) Marshall, V. C. (Dept. Surg., Royal Melbourne Hosp., Australia). *Aust NZ J Surg* 43(3):214-222, 1973.

In the past 8 years 15 of 151 recipients of cadaveric renal transplants at a hospital in Melbourne, Australia have developed skin lesions; eight of these 15 subsequently developed cancer. This represents a long-term hazard of therapy, and the risk appears to be cumulative. Of patients surviving for more than 4 years after transplantation, 28% have developed premalignant skin lesions and 17% have developed skin cancer. The fact that similar skin lesions developed in nine additional patients who did not receive transplants but who did receive similar immunosuppressive treatment for chronic renal or hepatic disease indicates that the complication is associated with the immunosuppressive agents rather than the transplantation procedure. Azathioprine and cyclophosphamide appear to show equal tendencies to stimulate the production of these tumors. Thus, immunosuppressive agents should not be used in nonmalignant conditions unless absolutely necessary, the morbidity of immunosuppression should be carefully considered prior to commencement of prolonged treatment, and renal transplantation patients should be cautioned against prolonged solar exposure. Suggested treatment for recurrent keratoses includes: reinforcement of protective and prophylactic measures; the use of local 5-fluorouracil cream; and the excision of any suspicious areas.

0391 SIALIC ACID ON LEUKEMIA CELLS: RELATION TO MORPHOLOGY AND TUMOR IMMUNITY. (E.) Reed, R. C. (Dept. Developmental Therapeutics, U. Texas, Houston), J. U. Gutterman, G. M. Mavligit and E. M. Herish. *Proc Soc Exp Biol Med* 145(3):790-793, 1974.

Blast cells from 25 patients with acute myelogenous leukemia (AML) and 10 patients with acute lymphoblastic leukemia (ALL) and mononuclear cells from 10 normal donors were treated with neuroaminidase and the amount of sialic acid released measured.

These values were correlated with the ability of the unmodified blasts to stimulate blastogenesis among autologous remission lymphocytes. In comparison with the normal mononuclear cells, uniformly low amounts of sialic acid were released from the leukemia lymphoblasts. This was correlated with a consistently poor ability of these cells to stimulate autologous lymphocytes. In contrast, the blasts from the AML patients released sialic acid in varying amounts. The myeloblasts which released excessively large amounts of sialic acid tended to stimulate autologous lymphocytes poorly when compared with the vigorous stimulation evoked by the cells releasing smaller amounts. The serum level of free sialic acid in the leukemia patients did not reflect the amount of sialic acid released from their blast cells.

0392 PRIMITIVE TERATOCARCINOMA CELLS EXPRESS A DIFFERENTIATION ANTIGEN SPECIFIED BY A GENE AT THE T-LOCUS IN THE MOUSE. (E.) Artzt, K. (Inst. Pasteur, Paris, France), D. Bennett and F. Jacob. *Proc Natl Acad Sci USA* 71(3):811-814, 1974.

Syngeneic immunization with primitive teratocarcinoma (PTC) cells has shown that such cells share a common early embryonic cell-surface antigen with mouse morula cells and male germ cells, notably sperm cells. Based on this finding, it was hypothesized that a wild-type gene at the T-locus might specify the antigen common to PTC, male germ, and morula cells. The implicated gene has a mutant form (t^{12}) which is lethal in homozygotes at the morula stage. Since mouse sperm cells express antigens determined by both wild-type and mutant t -alleles, specific anti-PTC antiserum was absorbed quantitatively with sperm from mice of various T genotypes ($+/+$ or $+/t^{12}$) and tested for residual cytotoxic activity on PTC cells. The results indicated that the major antibody component of the anti-PTC serum recognizes specifically the product of the wild allele $+t^{12}$. These results support the concept that genetically controlled differentiation antigens have essential functional roles during embryogenesis and the various stages of embryonic development are marked by the sequential appearance of specific cell surface components.

0393 NODULAR LYMPHOMA - EVIDENCE FOR ORIGIN FROM FOLLICULAR B LYMPHOCYTES. (E.) Jaffe, E. S. (Natl. Cancer Inst., Bethesda, Md.), E. M. Shevach, M. M. Frank, C. W. Berard and I. Green. *N Engl J Med* 290(15):813-819, 1974.

To investigate the cellular origin of nodular lymphoma, neoplastic cells from six patients with nodular lymphomas were studied in cell suspension and frozen tissue sections for the presence of: the C3 receptor - red cells coated with antibody and complement (IgMEAC) - of B lymphocytes; the receptor for cytophilic antibody - red cells coated with IgG (IgGEA) - of histiocytes; and the spontaneous rosette formation with sheep erythrocytes which is characteristic of T lymphocytes. A

high proportion of the neoplastic cells in suspension bound IgMEAC, but they did not bind IgGEA and did not form rosettes. In tissue sections of nodular lymphoma cells, the IgMEAC reagent bound to the neoplastic nodules. In control lymph nodes and spleens, these binding properties were shown to be characteristic of the cells of the lymphoid follicle, suggesting a follicular B-cell origin for nodular lymphomas.

0394 IMMUNOLOGICAL DETECTION OF ANTIGEN(S) ASSOCIATED WITH RAT COLON CARCINOMA. (E.)

Garmaise, A. B.-K. (Dept. Nutrition Food Sci., Massachusetts Inst. Technol., Cambridge), A. E. Rogers, P. M. Newberne, C. A. Saravis, H. Z. Kupchik and N. Zamcheck. *Nature* 248(5450):706-707, 1974.

Absorbed antisera to rat colonic tumors were reacted by the Ouchterlony technique with extracts of 1,2-dimethylhydrazine induced tumors, normal rat colon, and normal colon from tumor bearing rats. Reactions were obtained only with the tumor extracts. Counterimmunoelectrophoresis was performed on prototype agarose strips in which macromolecules from the colonic tumors and normal colon were electrophoretically transported to the absorbed antibodies. The results confirmed those obtained with the Ouchterlony technique. When seven two-fold serial dilutions of colonic tumor extract and normal colon extract were reacted with a constant concentration of antibody to rat colonic tumors, reactions were obtained with the tumor extract at all dilutions, but no reactions were obtained with dilutions of the normal colon extracts. Preliminary work indicated that the absorbed antisera reacted with rat fetal extracts, but the tumor antibodies do not appear to cross-react with human carcinoembryonic antigen (CEA) and rat tumor antigen does not appear to react with anti-CEA antisera. The antigen(s) found in the rat colonic tumors may provide a rat model for CEA in human colonic carcinoma.

0395 DETECTION OF NATURALLY OCCURRING ANTIBODIES TO RNA-DEPENDENT DNA POLYMERASE OF MURINE LEUKEMIA VIRUS IN KIDNEY ELUATES OF AKR MICE. (E.) Hollis, V. W., Jr. (Natl. Cancer Inst., Bethesda, Md.), T. Aoki, O. Barrera, M. B. A. Oldstone and F. J. Dixon. *J Virol* 13(2):448-454, 1974.

Specific antibodies to the RNA-dependent DNA polymerase (reverse transcriptase) of murine type C viruses were isolated from the renal glomeruli of both leukemic and nonleukemic AKR mice where they had presumably been deposited as immune complexes. The antibodies had sedimentation coefficients of 26S to 28S and 5S to 7S on sucrose rate zonal centrifugation. Inactivation with monospecific antisera to various mouse immunoglobulins identified the antibodies as being in both immunoglobulin (IgM and IgG) classes. In addition, these antibodies only reacted with the reverse transcriptase from murine and feline type C viruses, but not the polymerase from avian myeloblastosis virus (AMV).

These results indicate a lack of immunological tolerance and the presence of another immune complex system in AKR kidneys.

0396 CROSS-IMMUNITY BETWEEN CHEMICALLY-INDUCED SARCOMAS, DETECTED BY TRANSPLANTATION IN RESTRICTED GENETIC CONDITIONS. (E.)

Robert, F. (I.N.S.E.R.M., Res. Unit U95, Vandoeuvre, France), D. Oth and F. Dumont. *Eur J Cancer* 9(11/12):877-888, 1973.

Three sarcomas, TP8, TP4, and TP10 (the first being highly immunogenic and the last two being of lower antigenicity) were chemically induced in inbred Swiss/B mice. Swiss/B, (Swiss/B X C3H/He) F_1 , and (XVII X Swiss/B) F_1 mice were immunized with heavily irradiated fragments of these tumors and were challenged with viable tumor fragments. Specific immunization gave strong immunity, the immune reaction being more intense in the hybrids than in the Swiss/B strain of origin. Immunization with a mixture of TP4 + TP10 was unable to protect Swiss/B and (XVII X Swiss/B) F_1 mice against TP8, although this mixture elicited strong immunity against TP8 in the (Swiss/B X C3H/He) F_1 hybrids. Further, each of the individual tumors elicited some cross-reaction towards another in the (Swiss/B X C3H/He) F_1 hybrids. These results might be explained by the presence of at least two sorts of tumor associated transplantation antigens in these tumors: one unique for each individual tumor which is easily demonstrable in all cases; and one, possibly due to contamination with a common virus, which is recognized only in those animals which are not genetically tolerant to it.

0397 TRANSFORMATION BY SIMIAN VIRUS 40 OF SPLEEN CELLS FROM A HYPERIMMUNE RABBIT: EVIDENCE FOR SYNTHESIS OF IMMUNOGLOBULIN BY THE TRANSFORMED CELLS. (E.) Collins, J. J. (Harvard Med. Sch., Boston, Mass.), P. H. Black, A. D. Strosberg, E. Haber and K. J. Bloch. *Proc Natl Acad Sci USA* 72(2):260-262, 1974.

Spleen cells derived from a rabbit which had been hyperimmunized with a Type III pneumococcal vaccine were exposed to simian virus 40 (SV40) *in vitro*. After 114 days, transformed cells growing on the surface of one culture dish were observed and a cell line (TRSC-1) was established. The transformed cells had a morphology characteristic of cells transformed by SV40, contained the SV40-specific T antigen, and yielded infectious SV40 upon cultivation with indicator cells in the presence of Sendai fusion factor. The transformed cells incorporated labeled amino acid into protein with the antigenic properties of rabbit immunoglobulin G; the transformed cells produced only small amounts of this immunoglobulin. The results indicate that SV40 transformation of an immuno-competent cell such as a plasma cell or a lymphocyte resulted in a radically altered cell morphology as well as a change in growth characteristics; nevertheless, a specialized function, antibody production, was maintained.

0398 INDEPENDENT BEHAVIOUR OF BLOOD GROUP A- AND B-LIKE ACTIVITIES IN GASTRIC CARCINOMATA OF BLOOD GROUP AB INDIVIDUALS. (E.) Denk, H. (Sch. Med., U. Vienna, Austria), G. Tappeiner and J. H. Holzner. *Nature* 248(5447):428-430, 1974.

Five specimens of surgically removed gastric carcinomas from five patients belonging to the blood group AB were studied. Histologically, the tumors showed a variety of patterns ranging from well-differentiated adenocarcinomas to anaplastic globocellular growths. No relationship between the presence of blood group substances and the histological degree of differentiation was observed, and different distribution patterns of BG-A and -B activities were observed even in morphologically identical areas. No H activity was demonstrable in the tumors. Carcinoembryonic antigen has been postulated to result from the defective synthesis of blood group substances in gastrointestinal carcinomas due to genetic defects. The present results indicate that the selective loss of either BG-A or BG-B is most likely to be due to the deletion or repression of the corresponding gene (A or B) in the ABO locus. The disappearance of both A and B blood group substances in other parts of the same carcinoma indicates that the genetic and related enzyme defects vary even in the same tumor.

0399 TRANSFORMATION BY SIMIAN VIRUS 40 OF SPLEEN CELLS FROM A HYPERIMMUNE RABBIT: DEMONSTRATION OF PRODUCTION OF SPECIFIC ANTIBODY TO THE IMMUNIZING ANTIGEN. (E.) Strosberg, A. D. (Harvard Med. Sch., Boston, Mass.), J. J. Collins, P. H. Black, D. Malamud, S. Wilbert, K. J. Bloch and E. Haber. *Proc Natl Acad Sci USA* 71(2):263-264, 1974.

Extracts of spleen cells obtained from a rabbit which had been hyperimmunized with Type III pneumococcal vaccine and transformed with simian virus 40 (SV40) were subjected to agarose gel electrophoresis in the presence of an (125 I)S3 polysaccharide-protein conjugate. Binding of radioactivity in the gamma globulin region was observed. Extracts and media obtained from labeled cell cultures contained a protein that bound to an S3 but not to an S8 or inactivated S3 immunoadsorbent. After elution, the bound protein showed a single band on isoelectric focusing which corresponded in isoelectric point to one of the serum anti-S3 antibodies of the donor rabbit. These observations suggest that a normal committed lymphoid cell may be brought into continuous culture by virus transformation and still retain its ability to synthesize specific antibody.

0400 TRANSFER OF TUMOR-SPECIFIC DELAYED HYPERSENSITIVITY *IN VITRO* TO NORMAL GUINEA PIG PERITONEAL EXUDATE CELLS USING RNA EXTRACTS FROM SENSITIZED LYMPHOID TISSUES. (E.) Paque, R. E. (U. Illinois Med. Ctr., Chicago), M. S. Meltzer, B. Zbar, H. J. Rapp and S. Dray. *Cancer Res* 33:3165-3171, 1973.

Tumor-specific delayed hypersensitivity was

transferred to peritoneal exudate cells obtained from unimmunized Sewall-Wright strain 2 guinea pigs after the peritoneal exudate cells were incubated with RNA-rich extracts from the lymphoid tissues of syngeneic guinea pigs which had been immunized to either of two antigenically distinct diethylnitrosamine induced transplantable hepatomas. Tumor-specific delayed hypersensitivity was demonstrated by the inhibition of migration from the capillary tubes of the RNA-treated peritoneal exudate cells in the presence of the soluble tumor-specific antigen. The RNA extracts exhibited three distinct peaks corresponding to 4S, 18S, and 28S material when analyzed on sucrose density gradients. Tumor-specific delayed hypersensitivity was not transferred when: the RNA extracts were from the liver, muscle, or kidney of tumor-immunized guinea pigs; the RNA extracts were from unimmunized syngeneic guinea pigs; and the RNA extracts exhibited relatively large amounts of 4S material on sucrose density gradients as occurs after contact with RNase.

0401 EB VIRUS-ASSOCIATED ANTIBODIES IN CAUCASIAN PATIENTS WITH CARCINOMA OF THE NASOPHARYNX AND IN LONG-TERM SURVIVORS AFTER TREATMENT. (E.) De Schryver, A. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), G. Klein, W. Henle and G. Henle. *Int J Cancer* 13(3):319-325, 1974.

Sera from 30 Swedish patients with nasopharyngeal carcinoma (NPC) collected before or shortly after the commencement of therapy and from 24 long-term survivors (LTS) of NPC were tested for antibodies to Epstein-Barr virus (EBV) capsid antigens (VCA), to the D and R components of the EBV-induced early antigen (EA) complex, and to EBV-determined cell membrane antigens (MA). All patients had antibodies to VCA, with the incidence of high titers and the mean geometric titer increasing in the untreated patients with advance of the disease from stages I to III and IV. This relationship was not apparent in the LTS, in which the incidence of high anti-VCA titers and the geometric mean anti-VCA titer was about 1/2 as high as in the tumor-bearing group. The detectability and titers of anti-EA, especially the anti-D component, generally increased with an increase in the anti-VCA titers and with the advance in stage of the disease in the untreated patients. However, some patients had low anti-EA titers or none at all. The incidence and titers of anti-EA were distinctly lower among the LTS. Anti-MA, as determined by blocking of direct immunofluorescence, showed an increase in the geometric mean titer in the tumor-bearing patients from stages I to II, with intermediate values in the patients with stage III or IV disease. These results are in general agreement with previous observations made in Chinese NPC patients. However, there were considerable differences between the Swedish and Chinese patients with respect to the incidence and titers of antibodies to the D component of the anti-EA complex; this may reflect a reduced responsiveness of Caucasian NPC patients or a difference in the distribution of various types of the disease among ethnic groups.

- 0402 POSSIBLE ROLE FOR THE Fc RECEPTOR ON B LYMPHOCYTES. (E.) Ramasamy, R. (MRC Lab. Molecular Biol., Cambridge, England), A. Munro and C. Milstein. *Nature* 249(5457):573-574, 1974.

It is hypothesized that the Fc receptor on B lymphocytes is a membrane receptor (prereceptor) for the immunoglobulin which functions as antigen receptor on these cells. In general, there is an inverse correlation between the presence of surface immunoglobulin and Fc receptors on various cells derived from the plasma cell tumor line MOPC 21 (P3). This relationship is consistent with the proposed hypothesis provided that the surface immunoglobulin on the IgG secretor cells is not secreted immunoglobulin which has been passively absorbed from the culture medium; experimental evidence indicates that the surface immunoglobulin is not passively absorbed. Other cases in which Fc receptors may be exposed in the absence of immunoglobulin include: murine leukemias of non-T-cell origin which possess Fc receptors but no surface immunoglobulin; a light chain secreting variant of a plasmacytoma which is Fc receptor positive; and cells in patients with X-linked agammaglobulinaemia which lack surface immunoglobulin and possess Fc receptors. It is possible that the specific activation of B cells by antigen is mediated through prereceptors.

- 0403 NATURALLY OCCURRING CYTOTOXIC ANTI-TUMOUR ANTIBODIES IN SERA OF CONGENITALLY ATHYMIC (NUDE) MICE. (E.) Martin, W. J. (Zool. Dept., U. Coll., London, England) and S. E. Martin. *Nature* 249(5457):564-565, 1974.

Sera from athymic (nude) mice, which are almost completely devoid of θ -positive thymus-derived lymphoid cells, were tested for complement dependent cytotoxic activity against several tumor lines. The sera possessed significant complement dependent activity against all tumor cells but those of the PU-5 line (an ascites leukemia of BALB/c mice). When a pool of the sera was tested at several dilutions against the different tumor cell lines, the levels of cytotoxic activity were within the range of variation obtained with sera from normal mice. The sera from the nude mice showed no cytotoxic activity when tested on normal allogeneic spleen cells. These data demonstrate the capacity of the thymus-independent immune system to respond immunologically to tumor-associated antigens. It is possible that cytotoxic anti-tumor antibody production is partially maintained in normal and nude mice by the derepression of fetal and allo-antigenic components on nascent autochthonous tumors.

- 0404 SERUM INHIBITORS OF CELLULAR IMMUNITY IN HUMAN NEUROBLASTOMA. IgG SUBCLASS OF BLOCKING ACTIVITY. (E.) Jose, D. G. (Royal Children's Hosp. Res. Fdn., Melbourne, Australia) and F. Skvaril. *Int J Cancer* 13(2):173-178, 1974.

An autochthonous *in vitro* assay of cytotoxic

cellular immunity against neuroblastoma cells was used to measure the IgG subclass distribution of the specific blocking activity of sera from three children with untreated progressing neuroblastoma. These sera inhibited 90% of the cytotoxic activity of autochthonous lymphoid cells for their autochthonous neuroblastoma cells *in vitro*. Cross reactivity was demonstrated in serum blocking between different neuroblastoma patients, but sera from children with untreated Wilm's tumor or from normal adults inhibited less than 10% of specific neuroblastoma cytotoxicity. The major blocking activity in the *in vitro* autochthonous cytotoxic assay was associated with IgG₁, IgG₃, and, to a lesser extent, with IgG₄. Relatively poor blocking activity was found in association with IgG₂. Thus, IgG₁, IgG₃, and possibly IgG₄ may function as the antibody portion of a specific blocking factor in an autochthonous human neuroblastoma system.

- 0405 MIXED LYMPHOCYTE REACTIVITY AGAINST NORMAL CELLS BY SPLENIC LYMPHOCYTES FROM TUMOR-BEARING MICE. I. STUDIES OF VIGOROUS IMMUNE RESPONSIVENESS INDUCED IN F₁ MICE BY PARENTAL STRAIN TUMOR CELLS. (E.) Devlin, R. G. (Biochem. Dept., Mead Johnson Res. Ctr., Evansville, Ind.), J. D. McCurdy and P. E. Baronowsky. *J Exp Med* 139(1):224-229, 1974.

LI210 ascitic leukemic cells, which are of DBA/2 origin, were injected into female (DBA/2 X C57Bl/6)F₁ hybrid (BDF₁) mice, after which the splenic lymphocytes from the tumor-bearing animals were cultured with normal DBA/2 spleen cells in a two-way mixed lymphocyte reaction (MLR). The spleen cells from the tumor-bearing hybrids (BDFt) reacted vigorously in mixed lymphocyte culture with the mitomycin-treated normal spleen cells. The spleen cells from non-tumor-bearing BDF₁ mice reacted only weakly with these parental cells. The BDFt cells did not respond when cultured with mitomycin-treated spleen cells from the other parental strain. The vigorous MLR shown by the BDFt cells against the normal DBA/2 cells was not due to a double exposure of the reacting cells to histocompatibility antigens shared by the tumor cells and normal parental cells. The data suggest that spleen cells from leukemic mice may be able to induce an autoimmune-like process against host lymphocytes. Theoretically, such a phenomenon would considerably reduce an animal's ability to mount an immune attack against cells.

- 0406 MIXED LYMPHOCYTE REACTIVITY AGAINST NORMAL CELLS BY SPLENIC LYMPHOCYTES FROM TUMOR-BEARING MICE. II. STUDIES OF AUTOIMMUNE-LIKE ACTIVITY IN COMPLETELY SYNGENEIC AND SEMISYNGENEIC SYSTEMS. (E.) Devlin, R. G. (Biochem. Dept., Mead Johnson Res. Ctr., Evansville, Ind.), J. D. McCurdy and P. E. Baronowsky. *J Exp Med* 139(1):230-237, 1974.

LI210 ascitic leukemia cells, which are of DBA/2 origin, were injected into DBA/2 and (DBA/2 X C57Bl/6)F₁ hybrid (BDF₁) mice. When spleen cells from inoculated DBA/2 mice (DBAt cells) were cultured with

normal DBA/2 cells in a two-way mixed lymphocyte reaction (MLR), a vigorous immune reaction occurred. Normal DBA/2 cells reacted weakly or not at all to mitomycin-treated DBA/2 cells, while DBA/2 cells reacted vigorously with mitomycin-treated normal DBA/2 cells. Normal DBA/2 cells did not respond to syngeneic DBA/2 cells. Ascitic cells from L1210-bearing mice also responded to normal DBA/2 cells, and spleen cells from tumor-bearing BDF₁ mice (BDF₁ cells) responded to L1210 cells. Normal BDF₁ cells did not respond significantly to ascitic L1210 cells, although normal DBA/2 spleen cells respond significantly to mitomycin-treated L1210 cells. Normal BDF₁ mice responded significantly to mitomycin-treated splenic L1210 cells. BDF₁ cells, which respond vigorously to mitomycin-treated DBA/2 cells, did not respond to normal mitomycin-treated BDF₁ cells. These results suggest that spleen cells from tumor-bearing mice are able to induce cellular antilymphocytic autoimmunity in host animals.

0407 REDUCED TRANSPLANTABILITY OF SYNGENEIC TUMORS IN RATS IMMUNIZED WITH ALLOGENEIC TUMORS. (E.) Kobayashi, H. (Cancer Inst., Hokkaido U. Sch. Med., Sapporo, Japan), E. Gotohda, N. Kuzumaki, N. Takeichi, M. Hosokawa and T. Kodama. *Int J Cancer* 13(4):522-529, 1974.

Inbred Wistar-King-Aptekman/Mk (WKA) and Donryu rats were immunized with one to five s.c. injections of viable or inactivated syngeneic, allogeneic, or xenogeneic tumors or with allogeneic or xenogeneic normal liver, spleen, and/or kidney cells. In some experiments, the rats were X-irradiated. The growth of transplanted syngeneic tumors in both WKA and Donryu rats was suppressed by repeated immunization with tumors of allogeneic origin, with xenogenized tumors and tumors of xenogeneic origin proving less effective. Repeated immunization with normal organs also produced this effect, but only when organs of allogeneic origin were used. Immunization with syngeneic tumors artificially infected with murine leukemia virus also inhibited subsequent tumor growth. Optimum inhibition of growth was achieved with three immunizations. The inhibition of tumor growth was reduced by X-irradiation (600 R) in rats which had been immunized with either allogeneic or syngeneic tumors. Thus, inhibition by allogeneic tumor immunization may have been due to an immunological mechanism; the inhibition was very unstable at low radiation doses (200 R). The mechanism of inhibition may be associated with an increase in the nonspecific immunity of the host.

0408 IMMUNOLOGICAL STUDIES ON MALIGNANT MELANOMAS OF MAN. (E.) Romsdahl, M. M. (U. Texas M.D. Anderson Hosp., Houston) and I. S. Cox. *Yale J Biol Med* 46(5):693-701, 1973.

Gel diffusion studies to demonstrate immunological reactivity between putative tumor antigens in extracts from fresh melanoma tumors and sera from patients with malignant melanomas were not positive. Tumor eluates, which contained immunoglobulin G, often contained IgA and may have contained disassociated

antigen, enhanced melanoma target cell growth. Less pure tumor extracts, which presumably contained antigen-antibody complexes in addition to numerous proteins, were inhibitory to cell growth. The tumor eluates failed to enhance the growth of human sarcoma or muscle eluate preparations. An eluate prepared from a patient undergoing immunotherapy blocked the cytotoxic action of sensitized lymphocytes slightly more effectively than did an eluate prepared from an untreated patient; the former contained both IgG and IgA, while the latter contained only IgG. The results of a series of complement-fixing antibody studies indicate that the host may respond to the antigenic stimulation provided by a vaccine preparation.

0409 IN VIVO AND IN VITRO EVALUATION OF IMMUNE RESPONSE OF HAMSTERS TO IMMUNIZATION AND TRANSPLANTS OF AUTOCHTHONOUS RETICULUM CELL SARCOMA. (E.) Gerber, M. J. (U. Hlth. Sci./Chicago Med. Sch., Ill.) and E. R. Brown. *Cancer Res* 33(11):3029-3035, 1973.

Hamsters were immunized against reticulum cell sarcoma transplants using tumor-associated antigens (TAA) extracted by sonication from the tumor cells. After tumor cell challenge, 51.37% of the immunized animals completely rejected the tumor and 35.73% exhibited an increased latency period. All of the immunized animals exhibited cell-mediated immunity against TAA and blocking antibodies failed to develop in the sera of the immunized animals which developed tumors. In the Group 1 hamsters, which received a low inoculum, tumors developed as fast as in Group 3, which received a high inoculum. Several animals in Group 2, which received an intermediate inoculum, completely rejected the tumor and others exhibited an increased latent period. There was no immune response in the Group 1 animals, there was no blocking activity in the sera of the Group 2 animals which did not develop tumors (there was some blocking activity in the sera of the animals showing delayed tumor growth), and the Group 3 animals developed a cell-mediated immune response and exhibited a strong blocking activity in their sera. The appearance of blocking activity was closely related to the appearance of the tumor. Thus, immunization with TAA or a suitable amount of tumor transplant appeared to be capable of eliciting a beneficial cell-mediated response except when blocking antibodies were also present.

0410 TUMOR-ASSOCIATED ANTIGENS IN HUMAN MALIGNANT MELANOMA. (E.) Lewis, M. G. (Mem. U. Newfoundland, St. John's, Canada), P. J. G. Avis, T. M. Phillips and K. M. A. Sheikh. *Yale J Biol Med* 46(5):661-668, 1973.

Using immunofluorescence and complement-dependent cytotoxicity, a surface-membrane antigen has been detected in melanoma cells which appears to be highly patient specific with little or no reactivity at high titer; more weakly reacting membrane antigens which cross-react only at a very low intensity can also be detected. An anti-human fetal serum has recently been developed which reacts with human fetal cells and a number of human tumors (including malig-

nant melanoma) but not with adult human cells. Immunofluorescence has also shown the presence of cytoplasmic antigens which appear to be group specific in that positive sera from a number of melanoma patients cross-react widely with a number of melanoma cell preparations. Cross-reacting allogeneic sera are apparently of different sorts. The various antigens can be further studied using an illumination microscope system with a photoelectric measurement device. In studying the reactions of the antibodies against both cytoplasmic and membrane fluorescence in melanomas and other tumors, a rather wide scatter of fluorescence intensity was found. Visual microscopy showed that the highly fluorescent cells were plasma cells or lymphocytes which infiltrated the original tumor preparation. This may explain the multiple cross-reactivity seen when the tumor cells are not distinguishable from other cells carrying immunoglobulin. The autologous membrane antigen seems to be seen most in the early stages of tumor development. The autologous anticytoplasmic antibody appears next and may result from local destruction of the tumor. At a later stage of the disease, antibodies may be present against the allogeneic cytoplasmic antigen.

- 0411 CORRELATION BETWEEN THE SITES OF ANTIGENS DETECTED BY IMMUNOFLUORESCENCE AND ULTRASTRUCTURAL STAGES IN THE MORPHOGENESIS OF FV3. (Fr.) Braunwald, J. (Fac. Med., Strasbourg, France) and F. Tripiet. *C R Acad Sci (Paris)* 278(4):537-540, 1974.

Ultrastructural changes and the location of immunofluorescent antigens were studied after inoculation of frog virus 3 (FV 3) into 24-hr-old cultures of BHK 21 cells. One hr after inoculation many virions were adsorbed on the cytoplasmic membrane and small dense areas were situated near the membrane. A fluorescent border or fluorescent dots were present on the cell periphery, and fine fluorescent granules were detected inside of this. When cycloheximide (100 µg/ml) was added to the culture, most of the fluorescence disappeared along with the dense areas in the cytoplasm. This indicates that fluorescence observed in the early stages of infection is largely due to *de novo* protein synthesis and to viral adsorption on the cytoplasmic membrane. The protein synthesis probably occurs in the dense areas in the cytoplasm. Membrane fluorescence disappeared about 5 hr after inoculation, and the cytoplasm contained inclusions which appear to be viroplasms. Membrane fluorescence which appeared 14 hr after infection may be associated with the budding process by which the virions leave the cells. The very intense cytoplasmic fluorescence observed was due to viral antigens enclosed in pseudocrystalline areas.

- 0412 IMMUNE RESPONSES TO TUMOUR AND EMBRYO CELLS IN PATIENTS WITH MAMMARY CARCINOMA. (E.) Della Porta, G. (Natl. Inst. Tumor Res. Treatment, Milan, Italy), S. Canevari and G. Fossati. *Br J Cancer* 28(1):103-107, 1973.

Cytotoxicity microassays were used to study the cellular and humoral responses of mammary carcinoma patients against cultured target cells from breast

carcinomas and human embryos. Peripheral lymphocyte preparations from the breast cancer patients were cytotoxic on breast cancer cells in 75% of the cases and on embryo cells in 60-80% of the cases. Fifty-eight percent of the sera from the breast cancer patients exhibited a complement-dependent cytotoxicity when tested on the breast cancer cells; 33% of the sera collected 6 months after surgery exhibited cytotoxicity. Only one of the positive sera was cytotoxic on embryo cells. The immunosensitivity of the breast cancer cells to cancer patient lymphocytes was augmented by restraining cell growth with a decreased quantity of fetal calf serum prior to testing. Thus, patients with breast carcinoma respond immunologically to tumor associated antigens and the response is characterized by an ample cross reaction pattern at the cellular and humoral effector mechanisms.

- 0413 HARDING-PASSEY MELANOMA IN THE BALB/C MOUSE AS A MODEL FOR STUDYING THE INTERACTIONS BETWEEN HOST MACROPHAGES AND TUMOR CELLS. (E.) LeJeune, F. J. (Center Tumors, Free U., Brussels, Belgium). *Yale J Biol Med* 46(5):368-383, 1973.

Primary cultures were prepared from Harding-Passey melanomas (HPM) taken from the peritoneal regions of female Balb/c mice. The tumor consisted of numerous long, slim processes with fewer cells of a more regular shape containing large brown vacuoles. When subcultured, only the melanocyte type continued. When 100,000 or more HPM cells were inoculated i.p. into mice, all of the animals developed tumors. Small tumor growth was accompanied by an increase in the population of acid phosphatase positive peritoneal cells (PM) in both the tumors and the peritoneal cavity, while large tumor growth was accompanied by an intense macrophage infiltration with a decreased PM population. Mice were consistently protected against tumor graft by repeated inoculations of irradiated HPM cells. Spleen cells from immune animals strongly inhibited the uptake of tritiated thymidine by HPM cells. Normal unstimulated PM also had a marked inhibitory effect on thymidine uptake, whereas specifically immunized PM were less inhibitory. The repeated i.p. injection of irradiated HPM cells produced an increase in PM. Thus, the phagocytes which invade the Harding-Passey melanoma are host macrophages which are identical to those of the peritoneum macrophages.

- 0414 INDUCED MELANOMA REJECTION. (E.) Foster, M. (Dept. Zool., U. Michigan, Ann Arbor), J. Herman, L. Thomson and L. Eitzen. *Yale J Biol Med* 46(5):655-660, 1973.

Strong, systemic, and persistent antitumor immunity was induced in susceptible mice by administering alloantigenic normal spleen or liver tissue prior to contralateral tumor challenge. Two donor-recipient combinations were used: C57BL/6 allografts into BALB/c recipients, and A/J donors with congenic A.BY recipients. Both recipient strains are highly susceptible to the Harding-Passey (HP) melanoma. The allograft recipients, when challenged 1 wk later by

contralateral HP implantation nearly always rejected the first tumor challenges. The persistence of the antitumor immunity was indicated by the rejection of second and third tumor challenges, made as long as 102 and 88 days, resp., after the disappearance of the previous tumor. Xenografts from the deer mouse provided augmented tumor immunity, but these grafts were ineffective as allografts. Syngeneic tissue implants and allografts performed on the same day as the tumor challenged provided no significant antitumor protection.

- 0415 SURFACE MEMBRANE GLYCOPEPTIDES CORRELATED WITH TUMORIGENESIS. (E.) Glick, M. C. (Weizmann Inst. Sci., Rehovot, Israel), Z. Rabinowitz and L. Sacks. *Biochemistry* 12(24):4864-4869, 1973.

Glycopeptides were removed by trypsin from the surface membranes of the following cell types: hamster embryo cells transformed after treatment with the chemical carcinogen, dimethylnitrosamine; variants of these cells with suppression of the malignant transformed properties; and revertants of these variant cells to the transformed state. The glycopeptides were examined by gel filtration after Pronase digestion. In all cases, the gel filtration profiles of the fucose-containing glycopeptides were similar to those obtained from secondary hamster embryo cells. In contrast, profiles derived from tumors formed after inoculation into animals of all of these cell lines had the appearance of a specific group of glycopeptides not found in the original cells. Other properties characteristic of the transformed phenotype, such as ability to overcome contact inhibition and to form colonies with high efficiency in soft agar and liquid medium, failed to show a consistent correlation either with the nature of the surface glycopeptides or with the ability to produce tumors. These results demonstrate a change in the surface membrane glycopeptides with tumor formation and suggest a correlation between the two.

- 0416 SPECIFICITY OF CELLULAR IMMUNITY TO RENAL CELL CARCINOMA. (E.) Daly, J. J. (Urol. Serv., Massachusetts Gen. Hosp., Boston), G. R. Prout, Jr., C. A. Ahl and J. C. Lin. *J Urol* 111(4):448-452, 1974.

In a continuing study, the cellular immunity of three patients with renal cell carcinoma was tested *in vitro* against autochthonous renal tumor cells. In addition, the cellular immunity of these three patients plus two others with the same disease was assayed with allogeneic renal tumor cells. Lymphocytes from normal subjects and patients with cancers of other organs were assayed against the same target cells. Neither normal human lymphocytes nor lymphocytes from patients with nonrenal tumors proved cytotoxic to three cultured renal cell carcinomas. In each instance, the patient's own lymphocytes had significant cytotoxic effects on the tumor cells in the autochthonous series. In the allogeneic series, the lymphocytes of two patients proved cytotoxic to all exposed target cell lines and the lymphocytes of two other patients proved less cytotoxic to the target cells.

These results indicate the possible existence of a differential cytotoxic capability between autochthonous and allogeneic patients' lymphocytes for cancerous kidney cells. They also suggest that the cytotoxic activity of such effector cells may include a nonspecific, possibly quantitative factor which could account for the variability in responsiveness demonstrated by different patients and for the consistency of responsiveness demonstrated by one patient's lymphocytes.

- 0417 CYCLIC AMP LEVELS IN THE DEVELOPING HAMSTER FOETUS: A CORRELATION WITH THE PHASING OF FOETAL ANTIGEN IN MEMBRANE MATURATION. (E.) Rogan, E. G. (Dept. Microbiol., U. Tennessee, Knoxville), M. P. Schafer, N. G. Anderson and J. H. Coggin, Jr. *Differentiation* 1(3):199-204, 1973.

Antigens present in hamster fetus as late as 10 days post-coitus were found to elicit both humoral and cell-mediated immunologic reactivity against SV40-induced tumor cells in an adult syngeneic host; however, immunization with fetal cells of 11 days gestation or more was without effect. When fetal, neonatal, and adult hamster tissues were assayed for cyclic adenosine monophosphate (cAMP), the cAMP, which was present in low levels in the young fetus, was observed to increase markedly over the last 7 fetal days and to stabilize at birth. Thus, antigen silencing is coordinated with the rise in cAMP to adult levels. It is suggested that cAMP may be essential for the maintenance of the controlled growth characteristic of normal adult cells.

- 0418 SUBSTANCES IMMUNOLOGICALLY RELATED TO CEA. (E.) von Kleist, S. (Inst. Sci. Cancer Res., Villejuif, France). *Ann Immunol (Inst Pasteur)* 124 C(4):589-593, 1973.

Among the better known CEA-like substances are tumor associated antigen (TAA), colon carcinoma antigen III (CCA-III), a sulfoglycoprotein of fetal origin (FSA), X-substance, CE-X, and nonspecific cross-reacting antigen (NCA). NCA bears a strong physicochemical similarity to CEA, being distinguishable from the latter only by its lower molecular wt and its different specific antigenic determinants which appear to be located on the polysaccharide and protein moieties. There are two ways of determining whether the various CEA-like substances are the same or crossreacting with each other: exchange of reactants, and precise amino acid and carbohydrate analysis.

- 0419 IMMUNOCHEMICAL INVESTIGATIONS OF TISSUE α_2 -GLOBULIN IN NORMAL AND TUMOR TISSUES OF THE HUMAN KIDNEY. (E.) Prokopenko, P. G. (Dept. Biochem., N. I. Pirogov Second Moscow Med. Inst., USSR) and Yu. S. Tatarinov. *Bull Exp Biol Med* 76(8):977-979, 1973.

Tissue α_2 -globulin extracted from normal and cancerous human kidneys were studied immunochemically.

This protein, which had a molecular wt of $473,000 \pm 6000$, was about 10 times more plentiful in the cancerous kidney tissue than in the normal tissue. The tissue α_2 -globulin was also found in varying amounts in other normal human tissues and in human blood obtained at autopsy. It was not found in the blood sera of human fetuses, newborn infants, or healthy living adults. However, it was found in the blood of some living patients with carcinoma of the liver. Thus, malignant degeneration of the kidney may be accompanied by the accumulation of normal tissue α_2 -globulin in the tumor tissue.

- 0420 RADIOIMMUNOASSAY SYSTEMS FOR CEA. (E.)
Stevens, U. (Chester Beatty Res. Inst.,
London, England) and D. J. R. Laurence. *Ann Immunol*
(*Inst Pasteur*) 124C(4):615-617, 1973.

The low dose injection technique can be used to produce anti-carcinoembryonic antigen (CEA) antisera with comparatively low titers. When CEA and non-specific cross reacting antigen (NCA) are iodinated, only CEA binds detectably to this low titer antiserum when it is used in relatively low concentrations during radioimmunoassay; NCA binds at an antiserum concentration which is 20 times greater. The second antibody concentration required can be influenced by the presence of plasma in the direct test, and the total volume of the test system along with the ratio of total volume to sample volume vary widely from one test to another. Of the radioimmunoassay tests available, the direct double antibody methods are potentially the more rapid procedures, while the separation of antibody-bound antigen to the solid phase remains the most suitable assay system for CEA.

- 0421 STUDY OF CRITERIA FOR CELLULAR IMMUNITY
IN PATIENTS WITH MALIGNANT NEOPLASMS.
(Rus.) Govallo, V. I. (N. N. Priorov Ctr. Inst.
Traumatol. Orthopedics, Moscow, USSR), M. P. Grigor'eva and G. A. Kosmiadi. *Vopr Onkol* 19(11):18-21, 1973.

Cellular and humoral immunity were studied in 23 patients with a variety of tumors (adenocarcinomas of the lungs and breast, osteogenic sarcomas, Ewing's sarcomas, and chondrosarcomas). In 3-day-old cultures, phytohemagglutinin-stimulated lymphocyte transformation occurred in an average of $39.8 \pm 3.6\%$ of the cells from cancer patients compared with $71.9 \pm 4.1\%$ of cells from 50 normal controls. This inhibition of blast transformation was characteristic only of patients with malignant tumors and was not found among patients with benign tumors (osteoblastoclastoma) or autoimmune diseases (rheumatoid arthritis). Bach's spontaneous rosette formation with sheep erythrocyte suspensions was also inhibited in cancer patients (0.7-35 p.p.t. compared with 20-60 p.p.t. in controls). These findings suggest that carcinogenesis is associated with a deficiency of thymus-dependent lymphocytes or a decrease in their functional activity. After 5-7 days cultures of lymphocytes from cancer patients mixed with cells from normal donors had generally undergone complete cell lysis. In cancer patients leukocyte migration was inhibited by tumor antigen (extracts of osteogenic

sarcoma). Addition of autologous serum from cancer patients to the medium blocked this inhibition in most cases. Inhibition increased in only 2 of 11 cases. Both of these patients had osteogenic sarcomas which had been removed surgically and showed no signs of recurrence more than 6 months later. Humoral antibodies to human transplantation antigens were detected in 30% of the cancer patients. Since no relationship was found between the presence of these antibodies and blocking activity of serum in the leukocyte migration inhibition test or with the clinical course of the disease, the production of transplantation antibodies may be associated with multiple blood transfusions. Decreased cellular immunity and the presence of serum blocking factors in cancer patients may be of prognostic value and may indicate immunotherapy is needed to selectively stimulate thymus-dependent lymphocyte production.

- 0422 ABNORMAL ANTIERYTHROCYTE ANTIBODIES IN THE
COURSE OF HODGKIN'S DISEASE. (Fr.) Hoerni,
M. B. (Bergonie Fdn., Bordeaux, France), G. Hoerni-Simon and M. M. Durand. *Bordeaux Med* 6(12):1705-1708, 1973.

- 0423 REIMMUNOLOGICAL TEST FOR DETECTION OF MIN-
IMAL QUANTITIES OF SIMIAN VIRUS OB40. (Rus.)
Gonskii, G. M. (L. A. Tarasevich State Control Inst.
Med. Biol. Preparations, USSR). *Vopr Virusol* (2):235, 1973.

- 0424 PRODUCTION OF IMMUNOGLOBULIN OR GLUTAMINE
SYNTHETASE IN CELLS ORIGINATING FROM A
MOUSE MYELOMA. (Fr.) Jakob, H. (Dept. Cell Gene-
tics, Pasteur Inst., Paris, France) and F. Jacob. *Ann Immunol* (*Inst Pasteur*) 125C(1/2):351-352, 1974.

- 0425 PRESENCE OF CEA IN EXTRACTS OF PULMONARY
CANCERS. (E.) Sizaret, P. (Fac. Med.
Pharmacol. Dijon, France) and F. Martin. *Ann Immunol*
(*Inst Pasteur*) 124C(4):611, 1973.

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Med., Dijon, France). *Ann Immunol* (*Inst Pasteur*)
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- 0444 IMMUNOLOGIC REACTIVITY BETWEEN HUMAN TROPHOBLAST AND CANCER SERA: A PRELIMINARY REPORT. (E.) Park, H. S. (Honolulu, Hawaii). *Ann Allergy* 32(1):29-34, 1974.
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0449 ECTOPIC PRODUCTION OF THE ISOLATED ALPHA SUBUNIT OF THE GLYCOPROTEIN HORMONES. A QUANTITATIVE MARKER IN CERTAIN CASES OF CANCER. (E.) Rosen, S. W. (Clin. Endocrinol. Br., NIH., Bethesda, Md.) and B. D. Weintraub. *New Engl J Med* 290(26): 1441-1447, 1974.

0450 B-CELL AND T-CELL MARKERS IN LYMPHOID PROLIFERATIONS. (E.) Selifmann, M. (St. Louis Hosp., Paris, France). *New Engl J Med* 290(26): 1483-1484, 1974.

0451 EVIDENCE THAT MITOGENIC LECTINS INDUCE CHANGES IN LYMPHOCYTE MEMBRANE FLUIDITY. (E.) Barnett, R. E. (Dept. Chem., U. Minnesota, Minneapolis), R. E. Scott, L. T. Furcht and J. H. Kersey. *Nature* 249(5456):465-466, 1974.

0452 IMMUNOFLUORESCENCE OF PROTEIN SUBUNITS OF FERRITIN IN VARIOUS RAT CELLS *IN SITU* AND IN RAT HEPATOMA CELLS AND FIBROBLASTS IN CULTURES. (E.) Lee, J. C. K. (U. Rochester, N.Y.), S. S. Lee, K. J. Schlesinger and G. W. Richter. *Am J Pathol* 74(2):63a, 1974.

0453 INHIBITION OF NORMAL LYMPHOCYTE TRANSFORMATION BY LEUKEMIC SERUM. (E.) Humphrey, G. B. (Children's Mem. Hosp., Oklahoma City) and J. Lankford. *Exp Hematol* 1(5):276, 1974.

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0455 CHARACTERIZATION OF A CELL POPULATION IN PLASMA CELL LEUKEMIA (P.C.L.): IMMUNOGLOBULIN SECRETING CELLS WITH T-CELL PROPERTIES. (E.) Wetter, O. (U. Clin. Internal Med., Essen, Germany), M. van de Weert, N. Firusian and C. G. Schmidt. *Exp Hematol* 1(5):269, 1973.

0456 QUANTITATION IMMUNOGLOBULIN SITES OF LYMPHOCYTES FROM NORMAL SUBJECTS AND CHRONIC LYMPHOID LEUKEMIA. (E.) Binet, J. L. (Inst. Pasteur, Paris, France), G. Dighiero, J. Y. Follezou, T. Ternick and G. Vaugier. *Exp Hematol* 1(5):269, 1973.

0457 DETECTION OF TUMOR-SPECIFIC IMMUNITY IN NORMAL HOUSEHOLD CONTACTS OF TUMOR-BEARING PATIENTS. (E.) Byers, V. S. (San Francisco, Calif.), A. S. Levin and H. H. Fudenberg. *J Clin Invest* 53(6): 14a, 1974.

0458 CARBOHYDRATE AND PROTEIN ANALYSIS OF CARCINOEMBRYONIC ANTIGEN. (E.) Haverback, B. J. (Los Angeles, Calif.) and B. J. Dyce. *J Clin Invest* 53(6):32a, 1974.

0459 ISOLATION OF A NEW ONCOFETAL ANTIGEN FROM HUMAN MALIGNANT NEOPLASMS. (E.) Fierer, J. A. (Francis Delafield Hosp., New York, N.Y.), T. S. S. Mao and R. Appleton. *Am J Pathol* 74(2):62a, 1974.

See also:

- * (Rev): 0001, 0002, 0007, 0014, 0022, 0026, 0044, 0050, 0052
- * (Chem): 0123
- * (Viral): 0235, 0243, 0245, 0251, 0252, 0282, 0304, 0306, 0312
- * (Epid-Biom): 0485, 0512

- 0460 BERYLLIUM DISEASE. (E.) Stoeckle, J. D. (Massachusetts Gen. Hosp., Boston) and T. Mancuso. *Science* 183(4123):449, 1974.

Exposure to beryllium leading to new cases of beryllium disease still occurs even though a threshold limit value for safe exposure to the substance was established in 1950 by industry. Whether there is regular compliance with this limit of 2 micrograms/cubic meter or whether monitors accurately sample the beryllium concentration are frequent questions. Problems still exist regarding sampling techniques and different results may be obtained by using different methods. An epidemiologic study of employees in a beryllium plant indicated that age-adjusted mortality rates for lung cancer showed beryllium was an etiologic factor in its development. The rate of lung cancer was highest in those employees who had prior respiratory illness due to beryllium. Data also indicate that deaths among beryllium workers suffering from carcinoma of the liver and biliary tract may also be related to exposure. Delayed hypersensitivity to beryllium has been demonstrated in patients with chronic beryllium disease and in a small number of workers who did not appear to have the disease. This delayed hypersensitivity was demonstrated by showing a transformation *in vitro* of lymphoblasts to beryllium ions. The compensation received by workers who suffer injury due to exposure is slow in coming and inadequate in amount.

- 0461 HISTIOCYTIC MEDULLARY RETICULOSIS. (E.) Serck-Hanssen, A. (No affiliation). *Recent Results Cancer Res* 41:292-297, 1973.

Between 1964 and 1968, 23 cases (18 males, 5 females) of histiocytic medullary reticulosis were diagnosed among Ugandans. There were no specific gross findings, but the basic histology was remarkably constant, being characterized by the presence of large numbers of histiocytes diffusely throughout the reticuloendothelial system. Erythrophagocytosis was always seen in varying degrees. The liver, lymph nodes, and spleen were invariably involved, and occasional infiltrates of abnormal histiocytes were seen in organs such as the skin, lungs, and kidneys. Hemosiderin was found in all organs infiltrated by erythrophagocytic histiocytes. Diagnosis of the disease must take into account its similarity in some ways to infections such as typhoid; big-spleen disease; visceral, fulminant Hodgkin's disease; malignant lymphoma of the histiocytic type, and Letterer-Siwe's disease. The disease runs a fulminant course, with most patients dying within 6 months. The condition appears to be more common in Uganda than in temperate climates, and a high degree of stimulation of the reticuloendothelial system by various parasitic and bacterial agents may be a factor in its development.

- 0462 CARCINOMA IN THE GASTRIC STUMP AFTER PEPTIC ULCER SURGERY. (Ger.) Kivelitz, H. (Surg. Clin., Univ. Dusseldorf, Germany), E. Müller, F. Kleinschmidt and D. Loose. *Bruns Beitr Klin Chir* 220(3):253-258, 1973.

Of 944 patients who underwent gastrectomy for peptic ulcer in a 10-yr period, 39 (average age 62 yr) later developed stomach cancer. The latent period was shorter in older patients and averaged 22 yr. Carcinomas were located in the anastomosis in 46%, in the fundus in 41%, in the lesser curvature in 10.5%, and in the cardia in 2.5%. Of these 39 patients, 28 had undergone a Billroth II procedure, six a Billroth I procedure, and three a gastroenterostomy. Due to the relatively small number of cases, the high prevalence of stomach cancer associated with the Billroth II procedure might be fortuitous. Tumors were primarily adenocarcinomas and solid small-cell carcinomas with a few immature solid, scirrhous, and undifferentiated types and Gallert's carcinoma. Because of diffuse tumor infiltration or extensive lymph node and distant metastases, radical surgery could only be performed in nine cases. Death resulted from postoperative complications in 11 patients, including three who underwent radical surgery. Although the mean survival time was only 298 days, one patient has survived for 10 yr and another for 6 yr. Since patients with carcinomas of the gastric stump accounted for only 4.5% of all patients operated on for stomach cancer during this period, it cannot be claimed that gastrectomy predisposes a patient to stomach cancer. Because the latent period depends upon the age at which a patient undergoes gastrectomy, it is unlikely that there is a causal relationship between gastrectomy and stomach cancer. Gastrectomy should be performed for peptic ulcer when it is indicated because of the possibility that the ulcer will undergo malignant transformation.

- 0463 STUDIES ON THE MECHANISMS OF INVASION IN CANCER. III. PURIFICATION OF A NEUTRAL PROTEASE OF RAT ASCITES HEPATOMA CELL ASSOCIATED WITH PRODUCTION OF CHEMOTACTIC FACTOR FOR CANCER CELLS. (E.) Kono, M. (Kumamoto U. Med. Sch., Japan), K. Ushijima and H. Hayashi. *Int J Cancer* 13(1):105-115, 1974.

- 0464 A COMPARATIVE STUDY OF CYTOLOGY AND HISTOPATHOLOGY IN OROPHARYNGEAL TUMOURS. (E.) Pande, K. (Med. Coll., Nagpur, India), K. V. Moghe and U. Hardas. *Ind J Surg* 35(6):269-274, 1973.

- 0465 ACQUIRED (DIGITAL) FIBROKERATOMAS. COMPLICATION OF INGROWN TOENAIL. (E.) Herman, P. S. (Central U. Hosp., Sherbrooke, Quebec, Canada) and B. Datnow. *Acta Derm Venerol (Stockh)* 54(1):73-76, 1974.

- 0466 PSEUDOSARCOMATOUS CHANGES IN ANTROCHOANAL POLYPS. (E.) Smith, C. J. (U. Florida Coll. Med., Gainesville), R. Echevarria and C. A. McLelland. *Arch Otolaryngol* 99(3):228-230, 1974.

- 0467 PROGESTERONE HIGH LEVELS ACTION ON DYSPLASIAS AND CARCINOMAS *IN SITU* OF THE ENDOMETRIUM. (E.) De Brux, J. (Paris, France) and A. Schachter. *Acta Morphol Acad Sci Hung Suppl* 14:113, 1973.
- 0468 PATHOGENESIS OF HYPERPLASTIC POLYPS OF THE COLON: A HYPOTHESIS BASED ON ULTRASTRUCTURE AND *IN VITRO* CELL KINETICS. (E.) Hayashi, T. (Kuakini Hosp., Honolulu, Hawaii), R. Yatani, J. Apostel and G. N. Stemmermann. *Gastroenterology* 66(3):347-356, 1974.
- 0469 THE DISTINCTION BETWEEN GASTRIC ULCERATION AND CARCINOMA OF THE STOMACH. VALUE OF THE ERYTHROCYTE SEDIMENTATION RATE AND THE MAXIMAL ACID OUTPUT. (E.) Bock, O. A. A. (Dept. Med., U. Stellenbosch, Bellville, South Africa) and I. H. Boyd. *S Afr Med J* 47(28):1259-1260, 1973.
- 0470 TRACHEOBRONCHIAL EPITHELIAL MULTINUCLEATION IN MALIGNANT DISEASE. (E.) Chalon, J. (Albert Einstein Coll. Med., Bronx, N.Y.), J. S. Katz, S. Ramanathan, M. Ambavagar and L. R. Orkin. *Science* 183(4124):525-526, 1974.
- 0471 β -SITOSTEROLEMIA AND XANTHOMATOSIS. A NEWLY DESCRIBED LIPID STORAGE DISEASE IN TWO SISTERS. (E.) Bhattacharyya, A. K. (U. Iowa Coll. Med., Iowa City) and W. E. Connor. *J Clin Invest* 53(4):1033-1043, 1974.
- 0472 SMOOTH MUSCLE ORIGIN OF UTERINE PLEXIFORM TUMORS. ULTRASTRUCTURAL AND HISTOCHEMICAL EVIDENCE. (E.) Goodhue, W. W. (New York Hosp., New York), M. Susin and E. E. Kramer. *Arch Pathol* 97:263-268, 1974.
- 0473 MORPHOLOGICAL CRITERIA FOR ASSESSMENT OF HIGH RISK FOR BREAST CANCER. (Rus.) Neishtadt, E. L. (N.N. Petrov Res. Inst. Oncol., Leningrad, USSR). *Vopr Onkol* 20(2):3-11, 1974.
- 0474 HISTOPATHOGENESIS OF ELASTIC NEVI. (Ger.) Mausle, E. (Dermatol. Clin., U. Saarland, Homburg, Germany) and F. Nodl. *Arch Dermatol Forsch* 247(3):221-234, 1973.
- 0475 PRECANCEROUS PAPILLOMATOSIS OF THE GENITALS: TWO CASES. (Fr.) Barriere, H. (No affiliation), P. Litoux, B. Bureau, J. Welin and J. Le Treugilly. *Bull Soc Fr Dermatol Syphiligr* 80(4):388-392, 1973.
- 0476 HASHIMOTO'S DISEASE AND CANCER OF THE THYROID. (It.) Cavallari, A. (Inst. Surg. Pathol., U. Bologna, Italy), A. Cunsolo, and G. Pagliani. *Cancero* 24(4):183-187, 1971.
- 0477 MOLECULAR BIOLOGICAL ASPECTS OF TUMORIGENESIS. (Ger.) Munk, K. (German Cancer Res. Ctr., Heidelberg). *Verhandl Dtsch Ges Inn Med* 78:321, 1972.
- 0478 ULTRASTRUCTURAL ASPECTS OF THYMOMAS. (It.) Pozzuoli, R. (Inst. Pathol. Anat. Histol., Catholic U. Sacred Heart, Rome, Italy), M. Piantelli, P. Musiani and R. Mazzarella-Farao. *Arch Ital Anat Istol Patol* 44(3/6):183-189, 1972.
- 0479 HISTOPATHOGENETIC CONSIDERATION OF TWO RARE TUMORS OF THE CAUDA EQUINA. (It.) Muretto, P. (Inst. Pathol. Anat. Histol., U. Sassari, Italy). *Arch Ital Anat Istol Patol* 44(3/6):201-214, 1972.
- 0480 CHANGES IN THE MITOTIC ACTIVITY OF EPIDERMAL CELLS IN PSEUDOEPITHELIOMATOUS HYPERPLASIA AND SPINOCELLULAR CARCINOMA OF THE SKIN. (Rus.) Berenbein, B. A. (M. F. Vladimirovskii Regional Sci. Res. Clin. Inst., Moscow, USSR) and I. A. Kazantseva. *Vestn Dermatol Venerol* (8):25-28, 1973.
- 0481 ALVEOLAR CELL CARCINOMA. 3. GENESIS AND CHARACTERISTICS. (Ger.) Hackl, H. (Baumgartnerhohe Hosp., Vienna, Austria). *Zentralbl Allg Pathol* 117:241-256, 1973.

See also:

- * (Rev): 0010, 0032, 0034
- * (Chem): 0153, 0170
- * (Phys): 0219
- * (Viral): 0326
- * (Immun): 0393

0482 HYDATIFORM MOLE AND MALIGNANT TROPHOBLASTIC DISEASE IN ISFAHAN, IRAN. (E.) Sarram, M. (Ctr. Population Studies, U. Isfahan, Iran), M. Soleimanpour and A. Lofti. *Int J Gynaecol Obstet* 12(3):88-92, 1974.

Between 1970 and 1973, 72 patients with nonmetastatic and metastatic trophoblastic disorders were referred to the University of Isfahan, Iran gynecologic wards. Hydatiform mole (HM) was diagnosed in 67 cases; the other five cases presented with choriocarcinoma and a history of HM. Eleven of the HM patients developed chorioadenoma destruens or choriocarcinoma. The remaining 56 patients were discharged without malignancy. The average annual rate of HM was 22.85/1000 abortions and 7.58/1000 live births, while that of malignant trophoblastic disease (MTD) was 5.45/1000 abortions and 1.81/1000 live births. The mean rates of chorioadenoma destruens and choriocarcinoma were 0.67 and 1.13/1000 live births, respectively, and 2.04 and 3.41/1000 abortions, respectively. The general rule for treatment of HM patients is evacuation by Pitocin induction followed by curettage. Hysterectomy was performed in HM patients over 40 years of age and in patients showing evidence of choriocarcinoma or chorioadenoma destruens following HM. Chemotherapy was started in all patients who had persistent high human chorionic gonadotrophin titers after complementary therapy and in cases with radiologic evidence of pulmonary metastasis. The incidence of HM was high among teenage mothers who were primigravidas.

0483 ESTIMATION OF THE MEAN AND VARIANCE OF CYCLE TIMES IN CINEMICROGRAPHICALLY RECORDED CELL POPULATIONS DURING BALANCED EXPONENTIAL GROWTH. (E.) Jagers, P. (Dept. Math., U. Göteborg, Sweden) and K. Norrby. *Cell Tissue Kinet* 7(3):201-211, 1974.

A method of estimating the mean cell cycle time and the dispersion of cell cycle times in cultivated monolayer cell populations in balanced exponential growth is described. Experimentally, the method is based on cinemicrographic recordings of two normal human fetal cell lines (GP 115-2 and GP 117-1) and their simian virus 40 (SV40)-transformed counterparts. Mathematically, the analysis proceeds from the concept that any cell population in balanced exponential growth has a stable age-distribution which is related to the cycle time distribution, the incidence of cell loss, and the distribution of the times to disintegration of the disintegrating cells. Observations of the duration of time to disintegration, division, collision, or emigration of a randomly chosen cell (whichever occurs first) are then made and the mobility rate used to find the distribution of durations to death and the cycle time distribution. The resulting formulas are simple and considerably reduce the average cell observation time. The results of the experiments with the human cell lines indicated that the SV40-transformed cells have longer cycle times in spite of their shorter doubling times. The cell mobility was also increased in the transformed populations. These observations

confirm earlier findings, indicating that the extent of cell loss, rather than the length of cycle times, may play a decisive role in the (net) doubling time of cultivated cell populations.

0484 AN *IN VIVO* METHOD OF STUDYING THE KINETICS OF CELL PROLIFERATION IN NORMAL HUMAN EPIDERMIS. (E.) Allegra, F. (Dept. Dermatol., Parma U., Italy) and G. De Panfilis. *Acta Derm (Stockholm)* 54(2):87-90, 1974.

A method for evaluating the time required for DNA synthesis and the duration of the cell cycle among normal human epidermal basal cells is described. The method is based on the *in vivo* intradermal injection of 0.1 ml of tritiated thymidine into two areas of abdominal skin (one of which is treated twice). The two areas are then biopsied 1 hour postinjection. The mean percentage of labeled cells among six volunteer subjects was 3.79% in the area injected once and 4.80% in the twice-injected area. The DNA synthesis time for the epidermal basal cells was 7 hours and 35 minutes \pm 1.13 hours. The time required for the entire germinative cell cycle duration was 206.67 \pm 50.92 hours. Although this procedure is limited to the S phase and to the entire cell cycle duration, it is recommended for use in *in vivo* investigations in man.

0485 BCG VACCINATION AND ACUTE LEUKEMIA. (E.) Mathe, G. (Hosp. Paul-Brousse, Villejuif, France), F. Facy, F. Hatton and O. Halle-Pannenko. *Biomedicine* 27(3):132-134, 1974.

The incidence of BCG vaccination was compared among 126 hospitalized children with acute leukemia and a group of age-matched controls. There were no significant differences between the two groups in terms of the frequency of BCG vaccination (slightly higher among the leukemic patients), the vaccination techniques, or the positivity of tuberculin skin tests after vaccination. These data do not confirm the hypothesis that vaccination with BCG specifically applied against tuberculosis would decrease the incidence of leukemia before the age of 20 years. The mortality from spontaneous leukemia was then determined among a group of BCG-vaccinated (1 day after birth) AkR mice and a group of matched controls. The two groups did not differ significantly in terms of the rate of mortality from leukemia. Thus, the prophylactic effect on spontaneous leukemia has not been supported.

0486 CARCINOMA OF THE THYROID IN PATIENTS AGED 50 OR OLDER. (E.) Hoffman, E. (Dept. Surg., Sinai Hosp. Baltimore, Inc., Md.). *J Am Geriatr Soc* 22(4):151-166, 1974.

Carcinoma of the thyroid was studied in 60 patients aged 50 to 79 years (Series AA) and 185 patients of all ages (Series A). Carcinoma of the thyroid is fairly common among persons aged 50+ years, persons in this group constituting 32% of the cases in

Series A. In Series AA, the ratio of females to males was 5.7:1 versus 3.9:1 in Series A. In 18% of the elderly patients, the thyroid carcinoma was multifocal and was found incidentally during physical examinations in almost 2/3 of the cases. Radioiodine tracing was of little help diagnostically, the best criterion for diagnosis being suspicion on the part of the physician. If thyroid nodules are treated aggressively, the carcinoma can be diagnosed earlier. Often a preoperatively palpable nodule is not identified microscopically as being cancerous. Frozen-section diagnosis can be misleading; in 46% of the Series AA cases, the frozen section was reported as benign, while the permanent sections were found to be malignant. The treatment of choice is total thyroidectomy followed by radioiodine therapy if indicated. Thyroid substitution therapy should be started soon after surgery to prevent postoperative tetany and vocal cord paralysis. The mortality rate among the Series AA patients was 25%, with 15 deaths being due to secondary solid, anaplastic, follicular, or papillary metastases. Of 30 Series AA patients followed for 5 or more years after surgery, 10 had died of thyroid carcinoma, three were alive but with metastases, and 16 were alive and free of thyroid carcinoma.

0487 QUANTITATIVE CYTOLOGIC MEASUREMENTS IN HEPATOMAS. (E.) Gallagher, J. C. (VA Hosp., Bay Pines, Fla.). *Arch Pathol* 97(6): 392-394, 1974.

Quantitative measurements of nuclear-cytoplasmic ratios (N/C ratios) of hepatoma cells and control liver cells were made using an ocular micrometer. All specimens were from adult patients. All hepatomas were hepatocellular carcinomas. Measurements were made under oil at a magnification of 1,000. Generally, larger N/C ratios were found for hepatoma cells than for control cells. Hepatoma specimens could be distinguished from controls by the mean N/C ratio of 30 cells from each specimen. The variances of N/C ratios of hepatomas were larger than those of the controls, but some benign specimens with increased cellular regeneration also had large variances. Hepatomas had mean N/C ratios larger than 0.55, while those of the controls were less than 0.55. Quantitative cytologic measurements may have application to histopathologic interpretation of other types of invasive neoplasms, of intraepithelial neoplasms, and of borderline epithelial changes.

0488 THE BASHAMBAR NATH CHOPRA LECTURE (1971). EPIDEMIOLOGY OF ORAL CARCINOMA. (E.) Wahi, P. N. (Indian Council Med. Res., New Delhi). *Proc Indian Natl Sci Acad* 39B(1):24-31, 1974.

Indian morbidity figures for cancer show a predominance of oral and oropharyngeal cancers. Various factors have been noted to cause one segment of the population to be more exposed to a given carcinogen than other segments, resulting in geographical variations in cancer pathology. The cancers of the oral cavity are squamous carcinoma with varied morphological features conditioned

by exposure of the buccal mucosa to certain carcinogenic agents. Tobacco chewing appeared to be the most significant etiological factor. Persons with the habit of chewing tobacco daily had 8 times more risk of developing oral cancer than non-chewers. The earlier the habit started, the greater the risk. The more frequent the chewing, the greater the risk. A clear cut dose-effect relation was established. Of the 2 types of tobacco mainly used, one, called Mainpuri, was particularly dangerous as it is a mixture of tobacco leaf with lime, finely cut betel-nuts, camphor and cloves. Chutta smoking, prevalent in one area of India, involves a special variety of cherrot which is smoked with the burning end inside the mouth. A high incidence of palatal cancer is noted in this region. Among alcohol drinkers, frequency of oral cancer was 10 times greater than among non-drinkers.

0489 COMPARATIVE PROLIFERATIVE KINETICS OF CELLS FROM NORMAL HUMAN EPIDERMIS AND BENIGN EPIDERMAL HYPERPLASIA (PSORIASIS) *IN VITRO*. (E.) Chopra, D. P. (Temple U. Health Sci. Ctr., Philadelphia, Pa.) and B. A. Flaxman. *Cell Tissue Kinet* 7(1):69-76, 1974.

The proliferation kinetics of epidermal cells from normal human skin and psoriasis lesions (benign epidermal hyperplasia) were studied *in vitro*. Epithelial outgrowths were obtained from skin explants and the cell cycle was studied using the conventional method of following two successive curves of labeled mitosis after an initial pulse with ^3H -thymidine. For the normal epidermal cells the total cell cycle time (T_c) was 59 hours, the premitotic phase (G_1) was 39 hours, the duration of DNA synthesis (S) was 11.5 hours, the postsynthetic phase (G_2) was 7 hours, the duration of mitosis (M) was 1.5 hours, the labeling index (LI) immediately after the pulse was 10.5%, and the growth fraction (GF) estimated by continuous labeling was 66%. For the psoriatic cells T_c was 53.5 hours, G_1 was 38.9 hours, S was 6.5 hours, G_2 was 7 hours, M was 1.1 hours, and the LI immediately after the pulse was 12%. Continuous labeling of the normal and psoriatic cells gave similar maximum LI values. Thus the normal and psoriatic epidermal cells showed no significant difference in proliferative capacity.

0490 CANCER OF THE ENDOMETRIUM: AN IMPROVED EPIDEMIOLOGICAL ASSESSMENT. (E.) Bonham, D. G. (Postgrad. Sch. Obstetrics Gynaecology, U. Auckland, New Zealand) and R. J. G. Bonham. *Aust NZ J Obstet Gynaecol* 13(3):172-183, 1973.

A computerized life-table technique was used to follow up 535 patients with endometrial cancer. Although the rate of endometrial cancer was not higher among never-married women, the survival rate was significantly higher among married women than among never-married women. The survival rate was also higher among those diagnosed at earlier ages and among those diagnosed prior to menopause. Histologically, 47.3% of the cases were

well differentiated, 24.5% were undifferentiated, 7.8% were anaplastic, 10.7% were adenoacanthoma, 0.4% were pure squamous, and 2.6% showed borderline malignancy. More than 1/3 of the nonsurvivors died of other diseases. Although older women had a higher cancer specific mortality, they were able to live in near-equilibrium with the disease for a longer period of time than the younger women. In the younger women, surgery alone was superior to radiotherapy followed by surgery. The traditional 5-year and 10-year survival techniques obscure some important aspects of cancer epidemiology and should be replaced by life-table analysis.

0491 GENERAL ESTIMATE OF THE DISTRIBUTION OF
CANCERS IN BLACK SENEGALESE AFRICANS.

(Fr.) Sankale, M. (Fac. Med. Pharm., Dakar, Senegal), P. A. Menye and C. Quenum. *Union Med Can* 103(1):111-116, 1974.

Statistics obtained from three hospitals in Dakar showed that 3916 of 230,000 Senegalese blacks (1.7%) were hospitalized with cancer between October 1960 and July 1970. These patients came from all parts of Senegal and represented all ethnic groups and social classes. Cancer of gastrointestinal glands, primarily the liver, accounted for 26.30% of all cancer and was followed by cancer of the skin, primarily phagedenic ulcers (13.61%); female genitalia (11.49%); ears, nose, and throat (10.16%); hematosarcomas (9.39%); and breast (7.12%). Of these cancer patients, 56.20% were men and 43.80% were women. In contrast to Europe and America, cancer occurs primarily in the young adult: 62% of the patients were 21-50 yr and 50% were 31-50 yr old. Patients over 51 yr of age accounted for only 31% of the total. No particular predisposition to cancer was found for any ethnic group.

0492 A RESTRICTION POINT FOR CONTROL OF NORMAL
ANIMAL CELL PROLIFERATION. (E.) Pardee,

A. B. (Moffett Labs., Princeton U., N.J.). *Proc Natl Acad Sci USA* 71(4):1286-1290, 1974.

The relative positions between the M and S phases of the cell cycle of a number of different quiescent cell populations (BHK21/C13, J1(PYBHK), and Nil 8 cells) were investigated to determine whether they were at the same point within the G₁ phase. In one set of experiments, the cells in an exponentially growing culture were stopped and the kinetics of incorporation of (³H)thymidine measured after the addition of complete medium. In other experiments: one block was imposed on the cells, which were then shifted to another block to determine whether they are able to proceed to DNA synthesis; two blocking conditions were sequentially applied, after which the cells were put into complete medium and thymidine uptake measured; two blocking conditions were sequentially applied, after which the cells were put into low serum or isoleucine media; and variable intervals in complete medium were interposed between the two blocking conditions. The results indicated that cells which have reached quiescence by a variety of means are in the same

state. The data are consistent with the existence of a single switching point, the restriction (or R) point in G₁, that regulates the reentry of the cell into a new round of the cell cycle. When the cells were stopped by nonphysiological agents such as hydroxyurea or colchicine, they did not stop at the R-point. Normal animal cells may have evolved this ability to shift between proliferative and quiescent states as a mechanism for survival under conditions that lead to differentiation *in vivo*, or under nutritional deprivation to utilize this switching mechanism to achieve quiescence. A fundamental difference between normal and malignant cells may be that the malignant cells have lost their R-point control, so that their growth is less restricted.

0493 OBSERVATIONS ON THE CYTOKINETICS OF
CHRONIC MYELOID LEUKEMIA. (E.) Baccarani,

M. (Div. Haematol., U. Bologna, Italy), M. A. Santucci and S. Tura. *Haematologica* 57(11):672-685, 1974.

The mitotic index (I_m) and the *in vitro* ³H-thymidine flash labeling index (I_L) of the marrow and blood granulocytic precursors in chronic myeloid leukemia (CML) were determined in nine CML patients. The I_m and I_L of the marrow and blood promyelocytes and myelocytes (PMC and MC) did not differ from normal, and the I_L was equal in the marrow and blood in eight cases. The I_m and I_L of the marrow myeloblasts (MB) were lower than normal, and the I_L of the blood MB was lower than in the marrow MB in eight cases. In six patients the MB mitotic time (t_m) was longer than normal (as in acute leukemia), and in five patients the MB DNA-synthesis time (t_{DNA}) was shorter than 13.1 hours. The data suggest that the kinetic behavior of well differentiated granulocytic precursors (PMC and MC) is close to normal, whereas at the clinical onset of CML a fraction of the MB behaves as the leukemic blast cells of acute myeloid leukemia and the blastic crisis.

0494 MORTALITY FROM LUNG CANCER IN U.S. COAL
MINERS. (E.) Costello, J. (Appalachian

Lab. Occupational Respiratory Dis., Morgantown, W.Va.), C. E. Ortmeyer and W. K. C. Morgan. *Am J Public Health* 64(3):222-224, 1974.

Of 3726 Appalachian coal miners studied between 1962 and 1963, 451 had died by 1972. Neoplasm of the bronchus and lung accounted for 24 of these deaths, and neoplasms of the tongue and mouth accounted for none. The largest number of lung cancer deaths occurred in the 65-69 age year interval, while the 60-64 age year interval accounted for the largest number of deaths from all causes. The observed number of deaths due to lung cancer was low in the 55-64 year age brackets and high in the 65-69 year age bracket as compared with the death rate from lung cancer among U.S. males as a whole. Twenty-one of the 24 miners dying from lung cancer were and/or had been cigarette smokers. These results agree with previously published

British data in indicating a low standard mortality ratio for lung cancer among coal miners.

0495 OCCUPATIONAL LUNG CANCER AMONG COPPER SMELTERS. (E.) Kuratsune, M. (Dept. Public Health, Fukuoka, Japan), S. Tokudome, T. Shirakusa, M. Yoshida, Y. Tokumitsu, T. Hayano and M. Seita. *Int J Cancer* 13(4):552-558, 1974.

An unusually high lung cancer mortality rate among males in a certain town brought about a case control study on the basis of mortality cards. The case group consisted of 19 males who died from lung cancer and the control group included 19 males who had died of diseases other than cancer of the lung, urinary bladder, or skin. Of the 19 who had died of lung cancer, 11 had been employed as smelters in a local copper refinery. These smelters were undoubtedly exposed heavily to arsenic trioxide while employed, particularly during the years of the Second World War at which time safety conditions were not good. The validity of these diagnoses was checked by blind examination of chest X-ray films of the patients with occupational cancer, a group of other lung cancer patients, and the controls. The occupational cancer was diagnosed at a higher rate than the tumors of other lung cancer cases. In all the 11 cases, the disease had become manifest after the men had stopped working at the refinery, and none of them had been considered as having occupational cancer by their physicians, their previous employer, the authorities concerned, their families or their friends, or indeed, themselves. Such findings emphasize the need for a lifelong health care system for ex-smelters from copper refineries.

0496 RISE IN MORTALITY FROM TUMORS OF THE TESTIS IN JAPAN, 1947-70. (E.) Lee, J. A. H. (Sch. Public Hlth., Community Med., U. Washington, Seattle), M. Hitosugi and G. R. Petersen. *J Natl Cancer Inst* 51(5):1485-1490, 1973.

The mortality rates from malignant tumors of the testis among Japanese men were compared with those for white Americans for the period 1947 through 1970. During this period, the death rate from testicular cancer in Japan increased from 1.53/million to 3.81/million, the relative increase being greatest among the young adult population; the death rate among young adults and children is now greater than among the U. S. white population. Fatal testicular tumors among Japanese boys occur at a younger age than in white American boys. The rates in the middle-aged and elderly have also risen in Japan, although the death rates among these groups in the United States and Britain have fallen continuously since early in this century. The data indicate that the long-term risks for individuals are established early in life and are little affected by subsequent changes in the way of life. The increase in the Japanese mortality rate cannot be associated with particular years in the total period studied, but rather appears to be related to increased lifetime risks for those children born more recently.

0497 CERVICAL CARCINOGENESIS: AN EPIDEMIOLOGIC MODEL ADAPTABLE TO CONTROL PROGRAMS. (E.) Rotkin, I. D. (U. Illinois, Med. Ctr., Chicago). *Recent Results Cancer Res* 39:165-176, 1972.

An epidemiologic model of cervical carcinogenesis based on the multistage model is proposed. According to the model, the typical female at increased risk is from a rural or inner city background and is poor and not well educated. Her social setting dictates that as she enters adolescence she will begin her association with multiple sexual consorts; sexual union will lead to the transformation of susceptible cells in the cervical matrix, with the emergence of metaplastic or neoplastic epithelium from precursor cells which possess the potential or capacity for malignant transformation, perhaps by genetic susceptibility. A period of latency follows during which dysplasias and occasional *in situ* lesions may develop. Then, at a point during adulthood, a cocarcinogenic event is presumed to take place, after which the lesion is clinically detected if it induces symptoms and if care is available; altered hormonal secretion and/or some other substance or event may be cocarcinogenic. This model offers a timetable of predictable events upon which planning of primary and secondary prevention might be designed. Primary prevention would involve the short-term postponement of adolescent coitus, which would involve extremely difficult and complex social strategies. Secondary prevention would involve the detection of early disease in relation to developing morbidity; Papanicolaou smear test programs could be utilized. Adolescence and youth are the best periods for secondary intervention, but the smears should be continued at least until after the probability subsides that cocarcinogenesis has taken place. If intervention has not taken place and a developing lesion is clinically detected during adulthood, intervention takes the form of treatment. If the patient survives, there is a continuing need for rehabilitation and reassurance.

0498 MORTALITY FROM STOMACH CANCER IN COAL MINING REGIONS. (E.) Creagan, E. T. (Natl. Cancer Inst., Bethesda, Md.), R. N. Hoover, and J. F. Fraumeni, Jr. *Arch Environ Health* 28(1):28-30, 1974.

Mortality rates from stomach cancer and other neoplasms in coal mining areas of Utah and six other states were compared with those in comparable non-coal mining regions for the period 1950 through 1959. The regions were matched according to educational status. Among men, there were 969 deaths from stomach cancer (associated with lower socioeconomic class) in the mining regions, as compared with 721.6 deaths expected from rates in the control counties. Among women, there were 513 deaths from stomach cancer in mining regions, as compared with 446.9 deaths expected from the rates in the control counties. The excess mortality in the mining counties was slightly greater for men than women in all but two states. Among men in the mining areas, deaths were excessive from lung cancer (associated with lower socioeconomic class), but were significantly low from leukemia and cancer of the colon (associated with higher socioeconomic class).

omic class). Women in the mining areas had increased deaths from neoplasms of the cervix (associated with lower socioeconomic status) and lung, while mortality from breast (associated with higher socioeconomic class) and colon cancers was less than expected from the rates in the control counties. It is suggested that the observed mortality rates in the mining regions reflect some component of socioeconomic class rather than exposure to coal-related carcinogens.

0499 "FAMILIAL" HODGKIN'S DISEASE. (E.) Kintzer, J. S. (Geisinger Med. Ctr., Danville, Pa.) and R. H. Kough. *Bull Geisinger Med Ctr* 26(2): 53-56, 1974.

0500 INCIDENCE OF MALIGNANCY IN CHILDHOOD IN SOUTH INDIA. (E.) Fenn, A. S. (Christian Med. Coll. Hosp., Vellore, South India), A. Bakthaviziam, M. P. Reddy and A. Singh. *Ind J Surg* 35(6):262-268, 1973.

0501 COLPOSCOPIC ASPECTS OF ENDOCERVICITIS. (E.) Nunez-Montiel, J. T. (U. Hosp. Maracaibe, Venezuela), G. Gamero-Leon, H. Garcia-Galve, R. A. Molina, A. Lopez and C. Guerra. *J Reprod Med* 12(5): 197-203, 1974.

0502 THE SKIN CANCER AND PRECANCER MORBIDITY AMONG THE POPULATION OF NORTH OSETIA. (Rus.) Sheleshke, P. V. (North Osetia Med. Inst., Ordzhonikidze, USSR). *Vopr Onkol* 20(2):72-76, 1974.

0503 AN UNUSUAL CASE OF GONADIC GERMINAL TUMOR IN A BROTHER AND SISTER. (E.) Trentini, G. P. (Inst. Morbid Pathol., U. Modena, Italy) and B. Palmeiri. *Cancer* 33(1):250-255, 1974.

0504 CLONAL SELECTION, ATTENUATION AND DIFFERENTIATION IN AN *IN VITRO* MODEL OF HYPERPLASIA. (E.) Martin, G. M. (U. Washington Sch. Med., Seattle), C. A. Sprague, T. H. Norwood and W. R. Pendergrass. *Am J Pathol* 74(1):137-154, 1974.

0505 CARCINOMA OF THE STOMACH IN NEW MEXICO: A PRELIMINARY REPORT. (E.) Weitzner, S. (U. New Mexico Sch. Med., Albuquerque) and D. E. Smith. *Am Surg* 40(3):161-163, 1974.

0506 MALIGNANT MELANOMA IN EGYPT. (E.) El-Bolkainy, M. N. (Cancer Inst. Cairo U., Egypt) and A. M. Ebeid. *Tumori* 59(6):429-436, 1973.

0507 OCCUPATION OF FATHER AT TIME OF BIRTH OF CHILDREN DYING OF MALIGNANT DISEASES. (E.) Fabia, J. (Med. Sch., Laval U., Quebec, Canada) and T. D. Thuy. *Br J Prev Soc Med* 28(2):98-100, 1974.

0508 THE INCIDENCE AND CLINICAL SYMPTOMS OF ACUTE MYELOID LEUKEMIA IN CHILDREN. (Pol.) Klinowska, W. (Acad. Med., Wroclaw, Poland), E. Bohdanowicz and K. Hein. *Wiad Lek* 26(18):1673-1679, 1973.

0509 TUMORS OF THE CUTANEOUS ADNEXA IN BLACKS FROM WEST AFRICA. (Fr.) Sarrat, H. (Pasteur Inst., Dakar, Senegal), R. Camain and E. Grosshans. *Int J Dermatol* 13:139-148, 1974.

0510 MALIGNANT NASOPHARYNGEAL TUMORS IN TUNIS. (Rus.) Naumov, G. P. (Dept. Ear Nose Throat Dis., P. Lumumba Peoples Friendship U., Moscow, USSR). *Vestn Otorinolaringol* (4):84-87, 1973.

0511 THE OCCURRENCE OF FUNGI IMPERFECTA AND CHEMICAL COMPOSITION OF THE WATER AND SOIL IN THE ENVIRONMENT OF TUMOR PATIENTS IN THE VILLAGE OF LISZKI (KRAKOW REGION). (Pol.) Aleksandrowicz, J. (Acad. Med., Krakow, Poland), I. Gajda, T. Komornicki, K. Oleksynowa and B. Smyk. *Przegl Epidemiol* 27:409-415, 1973.

0512 SERUM CONCENTRATIONS AND GENETIC FACTORS OF IMMUNOGLOBULINS IN PATIENTS WITH NEUROBLASTOMA. (Ger.) Morell, A. (Inst. Clin. Exp. Tumor Res., U. Bern, Switzerland), F. Skvaril, H. Kaser and R. Scherz. *Schweiz Med Wochenschr* 104(18):663-665, 1974.

0513 EPIDEMIOLOGY OF HODGKIN'S DISEASE IN CHILDREN. A STUDY OF 36 CASES. (E.) Machado, J. C. (Dept. Path. Anat., APCC Ctr. Inst., Sao Paulo, Brazil), J. F. Da Silveira, Jr. and A. D. Russo. *Mem Inst Butantan* 35:55-61, 1971.

0514 NOMOGRAM FOR DETERMINING THE MEAN DIAMETER OF TUMORS BY THE SCHRECK FORMULA. (Rus.) Jordan, A. M. (L'vov Med. Inst., USSR) and G. V. Shishka. *Vopr Onkol* 20(2):92, 1974.

0515 CURRENT ASPECTS OF THE EPIDEMIOLOGY OF LEUKEMIA. (Rus.) Khokhlova, M. P. (Ctr. Inst. Hematol. Blood Transfusion, Moscow, USSR) and I. V. Osechinskii. *Sov Med* (8):18-23, 1973.

0516 COMPARATIVE STATISTICS FOR CANCER IN LAOS. (Fr.) Fontan, R. (Roy. Med. Sch., Vientiane, Laos) and E. Bouday. *Bull Soc Pathol Exot* 66(5):653-660, 1973.

See also:

* (Rev): 0020, 0021, 0023, 0031
* (Chem): 0077

0517 N^5 -METHYLTETRAHYDROFOLATE:HOMOCYSTEINE METHYLTRANSFERASE ACTIVITY IN EXTRACTS FROM NORMAL, MALIGNANT AND EMBRYONIC TISSUE CULTURE CELLS. (E.) Ashe, H. (Dept. Chem., U. California, Los Angeles), B. R. Clark, F. Chu, D. N. Hardy, B. C. Halpern, R. M. Halpern and R. A. Smith. *Biochem Biophys Res Commun* 57(2):417-425, 1974.

Malignant cells (J111, L1210, W-256) and human embryonic cells (FL) are unable to survive and grow when homocystine replaces methionine in tissue culture media containing excess vitamin B₁₂ and folic acid. The activity of N^5 -methyltetrahydrofolate:homocysteine methyltransferase was measured in extracts from these cell lines and from normal adult rat fibroblasts (L3-16) and normal adult rat thymus fibroblasts grown in medium containing methionine (0.1 mM), vitamin B₁₂ (2 mg/L), and folic acid (10 mg/L). Human amniotic cells also failed to grow when homocystine replaced methionine in the folic acid and cyanocobalamin rich medium. Extracts of J111, L1210, W-256, and FL cells grown in media containing methionine and adequate vitamin B₁₂ and folic acid had diminished N^5 -methyltetrahydrofolate:homocysteine methyltransferase activities in the absence of added cyanocobalamin when compared with extracts of normal adult rat cells. Extracts of human monocytic leukemia (J111) and FL cells have normal enzymatic activity in the presence of added cyanocobalamin, whereas the rodent malignant cells (W-256 and L1210) have abnormally low activity in the absence or presence of added vitamin B₁₂.

0518 ELECTRON MICROSCOPIC AND CYTOCHEMICAL OBSERVATIONS OF MAST CELLS CONTAINING MELANOSOMES IN BLUE NEVUS. (E.) Sato, S. (Dept. Dermatol., Sapporo Med. Coll., Japan) and A. Kukita. *Acta Derm (Stockholm)* 54(2):113-120, 1974.

The functional relationship between mast cells and melanocytes was studied via electron microscopy using biopsy specimens from the skin lesions of seven patients with blue nevus. Combined ultrastructural and cytochemical observations revealed no evidence of autochthonous melanogenesis by the mast cells distributed within these specimens. The melanosomes in these cells were mostly accumulated in the form of aggregates confined within membrane-bound vesicles which included masses regarded as mast cell granules. They appeared to have been taken up via heterophagocytosis for degradation rather than derived from the biosynthetic activities of these cells. These findings are consistent with previous reports indicating that mast cells in human skin are capable of ingesting extraneous materials. Acid phosphatase activity was demonstrated in the mast cell granules. It is still uncertain whether the single- and compound-type mast cell granules are closely related to primary lysosomes.

0519 REGULATION OF HUMAN BONE MARROW LEUCOPOIESIS. (E.) Golde, D. W. (Cancer Res. Inst., U. California, San Francisco) and M. J. Cline. *Br J Haematol* 26(2):235-241, 1974.

The role of colony-stimulating factor (CSF) in liquid phase normal human bone marrow culture was studied. Conditioned medium prepared from human peripheral blood monocytes had potent colony-stimulating activity when assayed in agar with normal human bone marrow. When monocyte-conditioned medium was added to bone marrow in liquid culture, no stimulation of marrow cell proliferation was observed. The stimulator did not affect the viable cell count or the differential cell count. When the bone marrow cells were removed from the liquid cultures and incorporated into agar overlays, they retained their colony-forming capacity for at least 2 weeks. Colony formation by the cells transplanted into agar was wholly dependent on a source of stimulation, although the cells left in liquid culture continued to proliferate without exogenously supplied CSF. Conditioned medium from liquid bone marrow cultures up to 21 days old had significant colony-stimulating activity, as did conditioned medium from monocytes and macrophages grown *in vitro*. These results indicate that bone marrow mononuclear cells provide CSF which supports the proliferation and differentiation of marrow elements in liquid culture.

0520 THE EPIDERMAL PROLIFERATIVE UNIT: THE POSSIBLE ROLE OF THE CENTRAL BASAL CELL. (E.) Potten, C. S. (Paterson Labs., Christie Hosp., Manchester, England). *Cell Tissue Kinet* 7(1):77-88, 1974.

The epidermal proliferative unit (EPU) for normal haired mouse (DBA-2) dorsal skin was defined using the superficial hexagonal cell to identify the basal cells of the unit. The model suggested in a two-compartment proliferative system comprising, on the average, a single stem cell per EPU and several secondary proliferative cells, whose divisions amplify to some extent the mitosis of the stem cell. These secondary cells are ultimately committed to differentiation (after a few divisions) and can therefore be referred to as "committed" cells. In the dorsal skin from male DBA-2 mice there are 10.6 basal nuclei beneath a column of cells. The central nucleus of the group responds slightly earlier and more effectively than the rest to stimulation, is cycling more slowly than the majority of the basal nuclei, and may spend significant periods of time out of cycle. The skin appears to contain a series of fairly independent proliferative units, each of which contains 10 of 11 basal nuclei and 8 to 10 superficial cells of which only the youngest one or two retain their nuclei. At the center of each group of basal nuclei is a cell which behaves differently from the rest and which is present in the skin in numbers compatible with the number of clonogenic cells; this repre-

sents the basic stem cell of the unit. The proposed model provides a simple unit of small size for use in the study of cell proliferation and its control.

- 0521 CFU-C YIELDS FROM THE HAEMOPOIETIC TISSUES OF NORMAL AND LEUKAEMIC RFM MICE. (E.) Gordon, M. Y. (Med. Coll. St. Bartholomew's Hosp., London, England) and J. E. Coggle. *Cell Tissue Kinet* 7(1):61-68, 1974.

Spleen and bone marrow cells from normal and leukemic RFM mice were assayed for colony forming cells in soft agar (CFU-C). During the development of myeloid leukemia, the maximum level reached by the bone marrow CFU-C was greater than that attained by the spleen CFU-C. This relationship was paralleled by the degrees of response shown by normal spleen and bone marrow cells plated *in vitro* with leukemic spleen and bone marrow "feeder" cells. These data suggest that the differences in relative yield are a reflection of qualitative differences between the normal precursor cells found in the spleen and bone marrow, rather than differences between the leukemic cells in these hemopoietic organs. The histological development of colonies grown from leukemic cells and the response of normal cells to leukemic feeder cells suggest that the colonies grown from the leukemic spleen and bone marrow cells are derived from the residual population of normal hemopoietic cells within the leukemic mouse. These results probably reflect an *in vitro* phenomenon rather than a parameter of cell population kinetics *in vivo*.

- 0522 FIBRINOGEN AND METASTASES. (E.) Laki, K. (Natl. Inst. Arthritis, Metabolism Digestive Diseases, Bethesda, Md.). *J Med* 5(1-3):32-37, 1974.

The growth of a malignant tumor can be compared to wound healing in that both start with clot formation and require subsequent vascularization. Malignant calls can also be compared with primitive, undifferentiated cells. Evidence indicates that cell differentiation goes hand in hand with oxidative metabolism, while fermentation, as the mode of energy production, comes into operation with the loss of differentiation. Although cancer cells retain some of their differentiation pattern, they, unlike normal tissue cells, have the ability to utilize fermentation for energy when the oxygen supply is reduced. By denying cancer cells the fibrin substratum needed for the capillaries to move into the growing tumor, it might be possible, by denying oxygen, to force the tumor cells into a primitive existence in which they would be more susceptible to cytotoxic agents. Experiments in which the clot stabilization process was inhibited indicated that implanted tumors in mice do not take or are retarded in growth, suggesting that a proper

fibrin network is essential for a solid tumor to develop. Thus, anticoagulants might be used along with cytotoxic agents in the treatment of cancer.

- 0523 FAMILIAL INCIDENCE OF JUVENILE POLYPOSIS COLI. (E.) Cathright, Jr., J. B. (Oschner Clin., New Orleans, La.) and T. W. Cofer, Jr. *Surg Gynecol Obstet* 138(2):185-188, 1974.

Juvenile polyposis coli is an hereditary disease with no apparent malignant potential. Symptoms, proctosigmoidoscopic findings, and barium enema findings are often confused with familial adenomatous polyposis, which has an inexorable progression to invasive cancer in most patients. Differential diagnosis is possible only through histological studies. One family's involvement with the syndrome was studied in detail. In treating the condition, sigmoidoscopy is of prime importance. It is suggested that polyps within reach of the sigmoidoscope be removed. For asymptomatic polyps beyond the reach of the standard sigmoidoscope, removal is not indicated. Operative intervention is rarely indicated in juvenile polyposis coli. In rare cases chronic anemia from blood loss may necessitate surgical intervention. Only if the polyps are too numerous to remove by multiple colotomies or colotomy and colonoscopy should resection of the intestine be considered.

- 0524 THE MEMBRANE JUNCTIONS IN COMMUNICATING AND NONCOMMUNICATING CELLS, THEIR HYBRIDS, AND SEGREGANTS. (E.) Azarnia, R. (U. Miami Sch. Med., Fla.), W. J. Larsen and W. R. Loewenstein. *Proc Nat Acad Sci USA* 71(3):880-884, 1974.

Human Lesch-Nyhan cells, which are coupling and have gap junctions, were fused with mouse cl-1D cells, which are noncoupling and lack gap junctions. The resulting hybrid cells were coupling and had gap junctions while they contained the nearly complete complement of parent chromosomes. As the hybrid cells lost human chromosomes, clones appeared among the segregants, which had reverted to the noncoupling and junction-deficient trait of the mouse parent cell. These results show a genetic correlation between the occurrence of coupling and of gap junction. They reveal that the human cell contributes a factor to the hybrids that corrects the junctional deficiency of the mouse cell. This factor is probably linked to one or more human chromosomes since loss of human chromosomes in the hybrids resulted in reversion to junctional deficiency. Thus it appears that the gap junction contains the coupling passageways in the present cell system. However, no proof is known that the gap junction is the universal or sole mediator of coupling.

- 0525 MYCETOMA FORMATION IN *TRICHOPHYTON RUBRUM* INFECTION. (E.) Burgoon, C. F., Jr. (Skin and Cancer Hosp., Philadelphia, Pa.), F. Blank, W. C. Johnson and S. F. Grappel. *Br J Dermatol* 90(2):155-162, 1974.
- 0526 PYODERMA GANGRENOSUM AND ACUTE MYELOBLASTIC LEUKEMIA. (Fr.) Bazex, A. (No affiliation), A. Dupre, J. Rigoulet, J. Bazex, J. L. Bonafe, J. Pris and G. Delsol. *Bull Soc Fr Dermatol Syphiligr* 80(5):440-447, 1973.
- 0527 BIOCHEMICAL DIFFERENCES IN DNA POLYMERASES IN LEUKEMIA CELLS. (Ger.) Rainer, H. (1st Med. Clin., U. Vienna, Austria), P. Hocker, E. Deutsch, A. Stacher and K. Moser. *Blut* 28(4):256-263, 1974.
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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	RNA	ribonucleic acid
i.m.	intramuscular	s.c.	subcutaneous
i.p.	intraperitoneal	sec	second(s)
IU	international unit(s)	U	unit(s)
i.v.	intravenous	UV	ultraviolet
kg	kilogram(s)	WBC	white blood cells (leukocytes), white blood count
LD ₅₀	median lethal dose(s)	wk	week(s)
m	meter(s)	wt	weight(s)
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		

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- 0601 NEW OBSERVATIONS ON FOLLICULAR LYMPHOMA.
(E.) Lukes, R. J. (U. Southern California Sch. Med., Los Angeles) and R. D. Collins. *Gann* 15:209-215, 1973.

Camera lucida studies of normal reactive follicular centers have indicated that they are composed of four cell types: cleaved cells, noncleaved cells, large cytoplasm phagocytes, and dendritic reticulum cells. The cleaved and noncleaved cells are considered to be part of the bursal equivalent of "B" cell system as plasma cell precursors. It is hypothesized that the small lymphocyte of the B cell system transforms into the noncleaved cell with intermediate cleaved cell stages. The follicular center in this system represents the site of memory induction for antigens associated with subsequent multiplication. Comparative camera lucida studies of follicular (nodular) lymphomas indicated that the lymphomas were composed of cleaved and noncleaved cells which were remarkably similar to those of normal follicular center cells, exhibiting only exaggerations in size and in the degree of nuclear cleavage. The follicular center cell lymphomas appear to represent either blocks in transformation or possibly a "switch-on" to one of the stages of transformation. A number of the recognized cytologic types can be related to the various stages in transformation. The majority of cases previously classified as reticulum cell sarcoma or histiocytic lymphoma appear to present features of noncleaved follicular center cells. It also appears that one or possibly two cytologic types of lymphoma may be identified as lymphomas of "T" lymphocytes on a morphological basis; more research is needed in this area. (8 references)

- 0602 CAUSES AND GENESIS OF MYELOID LEUKEMIA.
(E.) Sirtori, C. (G. Gaslini Inst., Genoa, Italy). *Haematologica* 57(11):612-620, 1973.

About 170,000 people per year die of leukemia, the incidence of which is higher among Mongoloid children, people exposed to benzene, atom bomb survivors, patients with polycythemia, Bloom's syndrome, and Fanconi's anemia, and identical twins of leukemic patients. Prenatal and early postnatal irradiation produce acute leukemia, while in the adult radiation tends to produce chronic myeloid leukemia. An increased incidence of myelocytic leukemia is reported among myeloma patients treated with Melphalan. The following chemicals are possible leukemogenic agents: pyrimidine, phenacetin, phenylbutazone, hexachlorocyclohexane, hexachlorophene, and phorbol. The glycoprotein "colony stimulating factor" produces granulocytosis and monocytosis in mice. Castration lowers the incidence of leukemia in male mice and accelerates plasmacytoma in females. There have been several instances of families with much higher than average incidence of leukemia. Cigarette smoke may be a factor in leukemogenesis, as may cyclic neutropenia. Chronic idiopathic leukocytosis appears to be negatively correlated with leukemia. An abnormal 22 chromosome, the Philadelphia chromosome, is present in most cases of chronic myeloid leukemia and absent in most cases of juvenile chronic myeloid leukemia. Leukemia cells contain ligases and poly-

merases not found in normal cells, and many leukemic cells lack the enzyme asparagine synthetase. In chronic myeloid and lymphoid leukemia there is a characteristic double-ring mitochondrial DNA, and leukemic cells differ from normal cells in terms of the tyrosyl and glutamyl transfer RNAs. Leukemic blood contained elevated levels of vitamin B₁₂. Leukemia resembles tumors in terms of the loss of cells through necrosis and the facilitated passage into the blood stream. (47 references)

- 0603 CHRONIC MYELOGENOUS LEUKEMIA: PRELEUKEMIA OR LEUKEMIA? (E.) Killmann, S.-Aa. (U. Hosp. Copenhagen, Denmark). *Haematologica* 57(11):641-649, 1973.

Chronic myelogenous leukemia (CML) in its initial phase is a cell hyperproduction syndrome which originates in a single cell and which bears many clinical similarities to polycythemia vera (PCV). However, while the prognosis with PCV is good, that with CML is poor due to the tendency in CML to blastic transformation. There are numerous data which show a close interrelationship between CML and acute myeloid leukemia (AML). Two lines of evidence indicate that the terminal acute myeloid leukemia in CML is present from at least the clinical onset of CML and that it does not develop secondarily later in the disease: the labeling index of myeloblasts with tritiated thymidine in CML as well as in AML is remarkably low at the onset of the disease, and in a recent case malignant myeloblasts were detected early in the course of CML. Thus, the best interpretation of CML is that it is a neoplastic process with progressively malignant properties. (28 references)

- 0604 CHROMOSOME ALTERATIONS IN CHRONIC MYELOID LEUKEMIA. PRESENT ASPECTS OF THE PROBLEM.
(E.) Baserga, A. (Dept. Internal Med., U. Ferrara, Italy) and G. L. Castoldi. *Haematologica* 57(11):621-640, 1973.

The Philadelphia chromosome (Ph¹) represents a marker in most cases of chronic myelogenous leukemia (CML), the Ph¹-negative forms of CML being somewhat different from the classical picture. During the acute transformation of CML, many numerical (hyperdiploidy) and structural (markers) karyotypic abnormalities are observable. A particular finding is the duplication of the Ph¹, which has been considered a forewarning of blastic crisis. Since Ph¹-like chromosomes have been found in several conditions other than CML, the Ph¹ might be better defined as a marker of the myeloproliferative syndrome rather than a characteristic of CML. On the basis of quinacrine staining studies, the Ph¹ appears to belong to a different chromosome pair than that to which the extra chromosome in Down's syndrome is generally assigned. This argues against the hypothesis that some genes located on the same chromosome pair are able to control the LAP (leukocyte alkaline phosphatase) activity, which is usually low in CML and high in Down's syndrome. The onset of the Ph¹ is commonly placed at the level of the stem cells of the myeloid system; probably only one or a few mutations

would be needed to produce the abnormality. Evidence indicates that the Ph¹ may not be a simple "by-product" of the leukemic proliferation. (71 references)

- 0605 CHRONIC MYELOID LEUKEMIA: ADVANCES IN CYTOCHEMISTRY. (E.) Quaglino, D. (Inst. Med. Path., U. Modena, Italy). *Haematologica* 57(11): 650-662, 1973.

There is evidence to indicate that two populations of granulocytes exist in chronic granulocytic leukemia: one consisting of leucocyte alkaline phosphatase (LAP)-negative leukemic cells, and one consisting of LAP positive nonleukemic cells. There is also evidence to support the hypothesis that the circulating granulocyte in chronic granulocytic leukemia may be characterized by cytoplasmic immaturity. In the blastic crisis the leukemic blast cells are characterized by a number of cytogenic abnormalities: the Sudan black B reaction is decreased in intensity; the PAS reaction in the immature cells of the blastic crisis differs from that of the chronic phase; the uptake of thymidine is reduced; and the pattern of uridine incorporation and uptake is altered. These findings indicate that a profound mutation occurs at the onset of the blastic crisis and is responsible for the observed abortive attempts at differentiation along different cell lines. It appears that leukemic blast cells are unable to give rise to mature granulocytes and that the LAP positive polymorphs often found in blastic crisis are derived from some residual clone of normal precursors situated either in the spleen or the bone marrow. (43 references)

- 0606 TUMOR IMMUNOLOGY: RECENT PROGRESS IN ETIOLOGY AND THERAPY. (It.) Aiuti, F. (Inst. Med. Clin III, U. Rome, Italy) and F. Franchi. *Progr Med (Roma)* 29(8):239-245, 1973.

A review is presented of some of the most important, unpublished papers presented at a symposium on "Immunological Aspects of Neoplasia" held in Houston. These include papers on new concepts of immune tolerance; the role of B lymphocytes in transplant rejection and their cytotoxic effect on tumor cells; interactions between cellular and humoral immunity in neoplasia; evaluation of the immune system in lymphatic leukemia; immunological diagnosis and the prognosis for gastrointestinal cancer; the pathogenesis of autoimmune disease, particularly lupus erythematosus; and antigens associated with herpes virus in the pathogenesis of human tumors. Research on immunotherapy is also considered. (20 references)

- 0607 CANCER AND OLD AGE: AN AUTOPSY STUDY OF 3,535 PATIENTS OVER 65 YEARS OLD. (E.) Suen, K. C. (Inst. Path., Kings County Hosp., Brooklyn, N.Y.), L. L. Lau and V. Yermakov. *Cancer* 33(4):1164-1168, 1974.

Between 1960 and the end of 1970, 3572 patients aged 66 years and over were autopsied at a Brooklyn, New

York hospital. One or more cancers were found in 1149 patients (32.55 of the necropsy population; the affected individuals included 743 males (40.3% of the male population) and 406 females (23.9% of the female population). The prevalence of cancer did not significantly change with age among the females, while the peak incidence in men was in the 76-85-year-old age group. There was a total of 1269 cancers, of which 1160 were carcinomas, 17 were sarcomas, and 92 were malignancies of the lympho-hemopoietic system. Cancer of the lung, prostate gland, and gastrointestinal tract constituted over 50% of the cancers. Cancer of the colon and rectum were the most common female cancers. Incidental cancers constituted 29% of the total cancers in this series, the prostate gland being the most common site of incidental cancers. The frequency of metastases decreased with age. More than one cancer were present in 9.6% of the cancer patients; the likelihood of developing another independent cancer increased with age among the cancer patients. The findings indicated that tumors are of a less aggressive nature in the elderly. (12 references)

- 0608 IN VITRO VERSUS IN VIVO METABOLIC ACTIVATION OF MUTAGENS. (E.) Malling, H. V. (Mutagenesis Br., NIH, Research Triangle Park, N.C.) and C. N. Frantz. *Environ Health Perspect* (6):71-82, 1973.

Dimethylnitrosamine (DMN) and diethylnitrosamine (DEN) are two nonmutagenic chemicals which, when exposed to mammalian metabolism, can form highly mutagenic products. For DMN the activation is microsomal, needs some cofactors, and the mutagenic activity of the product is directly correlated with the metabolic formation of formaldehyde with and without induction and across strains of mice. Formaldehyde does not contribute to the mutagenic activity of the reaction products. The variability between species and strains must be kept in mind when choosing a mammalian metabolizer of promutagens. Induction of microsomes may increase sensitivity in a given strain. At least with DMN and DEN, *Salmonella* G46 is far more sensitive than *Neurospora* as an indicator organism. The proximity of the indicator organism to the major site of metabolism is related to mutagenic activity in terms of orders of magnitude. The microsomal assay is a few orders of magnitude more sensitive than the i.p. host-mediated assay, and the intrahepatic host-mediated assay is a few orders of magnitude more sensitive than the *in vitro* microsomal system. (19 references)

- 0609 HOW EFFICIENT IS IMMUNOLOGICAL SURVEILLANCE AGAINST CANCER AND WHY DOES IT FAIL? (E.) Laroye, G. J. (Dept. Path., Cancer Inst., Toronto, Ontario, Canada). *Lancet* (7866):1097-1100, 1974.

While there is considerable evidence indicating that successful immunological surveillance against cancer occurs in man and laboratory animals, it is not clear how efficiently this mechanism protects against oncogenic events. The following factors may be involved in the frequent failure of immunological sur-

veillance: inherited selective defects of the immune response, mediated directly by Ir genes or through various mechanisms resulting in low-threshold tolerance; the absence of tumor-associated antigens; and the shielding of tumor-associated antigens. The currently poorly understood phenomenon of "sneaking through" may be caused by the shielding of the neoplasm from attack by immunocytes by the interposition of capillaries. Immunological surveillance should not be investigated by studying tumor immunity in cancer patients, in whom the existence of neoplasia is proof of the failure of such a mechanism. Healthy subpopulations at risk should be investigated, since they may include individuals who have effectively rejected a neoplasm. Direct cell membrane interactions, mediated through specific markers characterizing the various types of differentiated cells, may underlie a powerful nonimmunological mechanism of surveillance. This currently unexplored mechanism could provide new perspectives on the behavior of normal differentiated tissues as well as tumors. (34 references)

0610 CATECHOLAMINES IN HUMAN NEUROBLASTOMA CELLS. POSSIBLE DEFECTIVE STORAGE. (E.) Bohuon, C. (Gustave-Roussy Inst., Villejuif, France) and E. Comoy. *Biomedicine* 20(3):169-170, 1974. (10 references)

0611 CANCER AND THE OVARY. (E.) Percival, R. (London Hosp. Med. Ctr., England). *Proc R Soc Med* 67(5):381-387, 1974. (5 references)

0612 CANCER OF THE OVARY. (E.) Munnell, E. W. (Presbyterian Hosp., New York, N.Y.). *Proc R Soc Med* 67(8):797-798, 1974. (No references)

0613 CARCINOGENS IN THE ENVIRONMENT. (E.) Magee, P. N. (Middlesex Hosp. Med. Sch., London, England). *Proc R Soc Med* 67(8):741-743, 1974. (11 references)

0614 CARCINOMA OF THE LIP. ANALYSIS OF THE MATERIAL OF 25 YEARS. (E.) Molnar, L. (Natl. Inst. Oncol., Budapest, Hungary), P. Ronay and L. Tapolcsanyi. *Oncology* 29(2):101-121, 1974. (82 references)

0615 A POSSIBLE NITROGEN OXIDE-NITROSAMINE CANCER LINK. (E.) Fine, D. H. (Thermo Electron Corp., Waltham, Mass.), F. Ruffe, D. Lieb and S. S. Epstein. *Bull Environ Contam Toxicol* 11(1):18-19, 1974.

Based on studies of the short term effects of NO_x (nitrogen dioxide and nitric oxide), EPA has recommended that the NO₂ emission standards be relaxed. However, there is growing awareness that the N-nitrosamines, of which NO_x is a precursor, constitute a major class of carcinogens which are probably causally related to human cancer. Nitrogen oxides are readily absorbed by the body during inhalation. Although the efficiency of the *in vivo* conversion of NO_x to N-nitrosamines is unknown, if the conversion were 10% efficient, the amount of diethylnitrosamine which could be formed from 'clean' air would be carcinogenic. Thus, the nitrogen oxide levels recommended by EPA could pose significant public health hazards.

0616 TWO-STAGE MALIGNANT TRANSFORMATION OF RAT FIBROBLASTS IN TISSUE CULTURE. (E.) Lasne, C. (Inst. Sci. Res. Cancer, Villejuif, France), A. Gentil and I. Chouroulinkov. *Nature* 247(5441):490-491, 1974.

Cell cultures of embryonic fibroblasts from Wistar rats were treated with benzo(a)pyrene (initiator) and/or phorbol ester (promoter). Until the 21st passage, neither initiation alone nor initiation followed by promotion for six cell passages gave a marked increase in morphological transformation. Subsequently the incidence of morphological transformation increased sharply, particularly in the cells treated with both initiator and promoter. Although some cells treated with benzo(a)pyrene alone developed the ability to form small colonies, those subsequently grown in media containing phorbol ester often developed into dense foci. Progressively growing tumors regularly developed only in those animals injected with cells which had been treated with both benzo(a)pyrene and phorbol ester. Cells which had been treated with initiator alone occasionally gave rise to more slowly growing tumors. Cells treated with phorbol ester showed a low colony-forming ability and did not give rise to tumors in living animals. These results provide evidence for two-stage malignant transformation *in vitro*.

0617 DETERMINATION OF BENZO(a)PYRENE IN SMOKE CONDENSATES BY HIGH PRESSURE RAPID LIQUID-LIQUID CHROMATOGRAPHY. (E.) O'Hara, J. R. (Stange Co., Chicago, Ill.), M. S. Chin, B. Dainius and J. H. Kilbuck. *J Food Sci* 39(1):38-40, 1974.

A method has been developed for the determination of benzo(a)pyrene in smoke condensates by high pressure rapid liquid-liquid chromatography (LLC). Aqueous soluble smoke flavors are extracted with iso-octane and washed with 5% NaOH, water, and 2N sulfuric acid. The resinous smoke condensates are dissolved in 20% NaOH or 70% acetic acid, extracted with iso-octane, and washed with 5% NaOH, water, and 2N sulfuric acid.

The vegetable oil soluble smoke flavors are extracted with isooctane and washed with 85% H₃PO₄ and 5% NaOH. The extracts are then cleaned up by column chromatography and developed using thin-layer chromatography and LLC. The sensitivity limit of the LLC ultraviolet detector for benzo(a)pyrene is 0.015 g. The recovery of benzo(a)pyrene added at a level of 10 ppb was 74-88% for aqueous smoke, 60-81% in resinous smoke condensates, and 68-84% in oil soluble condensates as determined by LLC. LLC allows the individual separation and quantitation of benzo(a)pyrene and benzo(e)pyrene, and offers the investigator a highly reproducible and reliable method of quantifying the polycyclic aromatic hydrocarbons in smoke condensates.

0618 NITROSOCARBARYL AS A POTENT MUTAGEN OF ENVIRONMENTAL SIGNIFICANCE. (E.) Elespuru, R. (Oak Ridge Grad. Sch. Biomed. Sci., U. Tennessee), W. Lijinsky and J. K. Setlow. *Nature* 247(5440):386-387, 1974.

The mutagenicity of nitrosocarbaryl (NC) was compared with that of nitrosomethylurethane (NMUr) and N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) using two bacterial systems, *Escherichia coli* and *Haemophilus influenzae*. In general, the mutation rate increased as a function of mortality up to a loss of about 90% of the cells, after which the observed mutation frequency leveled off and then declined. The molar concentration of NC required to induce a mutation frequency of 10⁻⁵ was less than 1/50 the concentration of MNNG required, and less than 1/10 the concentration of NMUr required to induce a similar level of mutation. The precursor of NC, carbaryl, was not mutagenic. The presence of the naphthyl group on NC, which increases its lipid solubility, appears to be a factor in its biological activity. *E. coli* was less sensitive than *H. influenzae* to both MNNG and NC, with NC being a more potent mutagen than MNNG in both systems. NC constitutes a possible hazard to man, since its precursors carbaryl and nitrite are common environmental constituents which are ingested, and the stomach provides the acidic conditions for its formation.

0619 TUMOR DEVELOPMENT AFTER 3-METHYLCHOLANTHRENE IN IMMUNOLOGICALLY DEFICIENT ATHYMIC-NUDE MICE. (E.) Stutman, O. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.). *Science* 183(4124):534-536, 1974.

3-Methylcholanthrene (MC) (0.1 mg) was administered at birth to athymic-nude (nu/nu) and normal heterozygous (nu/+) mice, which were subsequently maintained in a relatively pathogen free environment. No significant differences in tumor incidence or latent period for tumor development were observed between the two strains. All tumors were fibrosarcomas originating at the site of MC injection. The strains did not differ in terms of MC toxicity. MC had no effect in prolonging allogeneic skin graft (from DBA/2 mice) rejection times in the nu/+ mice. All of the MC and control nu/nu mice retained viable grafts until the end of the experiment, 80 days later. The nu/nu and nu/+ mice did not differ in terms of the incidence of number of long adenomas following MC

treatment. The results indicate that the absence of an intact thymus-dependent immune system may not affect significantly the risk for solid tumor development after exposure to MC at birth, thus arguing against an active role of thymus-dependent immunity as a surveillance mechanism preventing tumor development.

0620 LONG TERM EFFECTS OF AFLATOXIN B₁ AND VIRAL HEPATITIS ON MARMOSET LIVER. A PRELIMINARY REPORT. (E.) Lin, J. J. (U. Kansas Sch. Med., Kansas City), C. Liu and D. J. Svoboda. *Lab Invest* 30(3):267-278, 1974.

Marmosets (36) were divided into 4 groups with group 1 receiving a diet containing 200 µg/kg aflatoxin B₁, group 2 receiving the aflatoxin B₁ diet plus virus injections containing hepatitis agent 6 weeks after the start of the diet, group 3 receiving only the hepatitis agent, and group 4 serving as controls. Long term observation of the effects of aflatoxin B₁ and viral hepatitis on marmoset liver in terms of morphologic and chemical changes were noted. Viral hepatitis alone did not induce liver cirrhosis and/or hepatic tumors in nonhuman primates, but did result in occasional stellate portal fibrosis of the liver. In aflatoxin B₁ injury, marmosets had cirrhosis in addition to hepatic tumors. The double injury of aflatoxin B₁ and viral hepatitis produced more severe effects on marmoset liver than when the animals were injured with a single agent. Cirrhosis was much more severe, but transaminase elevation did not show an additive affect with double injury in the acute stage. Hepatic injury was parallel to the dose of aflatoxin B₁. Males were more sensitive to aflatoxin injury. Ultrastructural changes of hepatocytes were reversible on withdrawal of aflatoxin. Hepatic tumors appeared late in these studies. Tumors were histologically indistinguishable from malignant liver tumors induced by aflatoxin in rats; therefore, it is believed that, if the marmoset had lived longer, distant metastasis could have developed in some of these animals.

0621 DEVELOPMENT OF CARCINOMA OF THE LUNG AS REFLECTED IN EXFOLIATED CELLS. (E.)

Saccomanno, G. (St. Mary's Hosp., Grand Junction, Colo.), V. E. Archer, O. Auerbach, R. P. Saunders and L. M. Brennan. *Cancer* 33(1):256-270, 1974.

Cytologic examinations were performed on sputum samples which were collected periodically beginning in 1957 from a group of active underground and surface uranium workers. Many of these individuals developed abnormal squamous cell metaplasia that gradually progressed in several workers to invasive carcinoma. The progression was from mild, moderate, and marked atypical squamous cell metaplasias to carcinoma *in situ*. Cigarette smoking and uranium mining were both associated with the prevalence of these atypias and with carcinoma *in situ* and invasive cancer. Neither variable was strongly associated with the duration of the various stages of atypia, however. Age at beginning uranium mining was more closely associated with

age at the development of carcinoma *in situ* than any other factor studied. The average duration between the appearance of marked atypia and invasive carcinoma was 3 to 4 years. Periodic sputum surveillance of groups at high risk of developing bronchogenic cancer can utilize this period for early detection and treatment.

0622 CHROMOSOMAL EXAMINATION OF VARIOUS CELL CLONES (IN VITRO) DERIVED FROM A DMBA (7,12-DIMETHYL- α -BENZANTHRACENE)-INDUCED MALE RAT BREAST TUMOUR. (E.) Bishun, N. P. (Marie Curie Mem. Fdn., Surrey, England), J. Mills, N. Lloyd and D. C. Williams. *Eur J Cancer* 9(11/12):865-870, 1973.

A mammary tumor originated in 1 male of a group of 72 DMBA-treated (20 mg in 1 ml oil) male Sprague-Dawley rats. The tumor was set up in a culture and the cells cloned 13 times. Both explants and minced tissues grew well with mainly rounded cells with distinct nuclei and well defined borders. They were epithelial-like and grew as confluent sheaths. Several clones were identified from the original tumor cells in culture. The chromosomes differed slightly as to chromosomal mode, but they all contained 2 constant marker chromosomes, one telocentric and one submetacentric. Ten of 13 clones were re-injected into cortisone prepared rats, but only 5 of these subsequently formed tumors in the animals. The chromosomes of the latter tumors showed no significant shift in modal numbers or change in the number of marker chromosomes. These results provide further evidence in support of the stem line theory of cancer development.

0623 ARLY HYDROCARBON HYDROXYLASE INDUCIBILITY AND BRONCHOGENIC CARCINOMA. (E.) Kellermann, G. (Sect. Med. Genetics, U. Texas, Houston), C. R. Shaw and M. Luyten-Kellerman. *New Engl J Med* 289(18):934-937, 1973.

Aryl hydrocarbon hydroxylase is an inducible, membrane-bound enzyme involved in the metabolism of chemical carcinogens. The extent of aryl hydrocarbon hydroxylase induction in cultured human leukocytes is under genetic control. The normal white population of the United States can be divided into 3 distinct groups with low, intermediate, and high inducible aryl hydrocarbon hydroxylase activities with frequencies of 44.7%, 45.9%, and 9.4%, resp. A group of 50 patients (46 white males and 4 white females, aged 38-85 yr) with bronchogenic carcinoma were studied, and the frequencies of the 3 groups were 4.0%, 66.0%, and 30.0%, resp., which suggests that susceptibility to bronchogenic carcinoma is associated with the higher levels of inducible aryl hydrocarbon hydroxylase activity. A tumor control group consisting of 57 persons including 3 with melanoma, 3 with Hodgkin's disease, 4 with head and neck cancer, 2 with breast cancer, 1 with uterine cancer, 12 with bladder cancer, 2 with prostate cancer and 7 in which the primary tumor was unknown was similarly studied. The tumors in these individuals did not appear associated with increased amounts of aryl hydrocarbon hydroxylase inducibil-

ity. All of the lung cancer patients were heavy smokers. These present findings add support to the concept that epoxides are the metabolically activated and ultimately carcinogenic forms of polycyclic hydrocarbons.

- 0624 THE GENETIC PROCESS IN THE PREMITOTIC PERIOD AND FORMATION OF CHEMICALLY INDUCED CHROMOSOME ABERRATIONS. (Rus.) Dubinin, N. P. (Inst. Gen. Genetics, Moscow, USSR), A. P. Akif'ev, L. G. Dubinina and A. K. Ergashev. *Dokl Akad Nauk SSSR* 214(1):197-200, 1974.

When dry seeds of *Crepis capillaris* were incubated with 5-fluoro-2-deoxyuridine (FUDR) and a deficient quantity of thymidine, FUDR increased the number of chromosome mutations in the postsynthetic (G_2) phase. However, when *Crepis capillaris* seeds were treated with an aqueous solution of nitrogen mustard ($7.5 \times 10^{-5}M$) in the G_1 phase, the number of chromosome aberrations found after incubation with equimolar quantities of FUDR and thymidine ($5 \times 10^{-5}M$) decreased by about 66-100%. An analysis of structural mutations induced by nitrogen mustard revealed that the frequency of chromatid deletions and rearrangements differed. Aberrations involving recombination were clearly the most common of the isolocus rearrangements. The sensitizing effect of FUDR is associated with a large increase in the number of simple and isolocus breaks since no appreciable change occurred in the number of rearrangements. When thymidine was added to the medium before mitosis, the decrease in structural mutations resulted largely from a decrease in chromatid deletion, chromatid rearrangements, and isolocus breaks with recombination. Thymidine had a protective effect when it was present in the medium for 2, 1.5, and 1 hr before fixation. This is the first demonstration that the number of structural chromosome mutations induced by nitrogen mustard can be reduced for a long period after exposure to the mutagen. It is suggested that the presence of exogenous thymidine causes additional DNA synthesis and thus shortens the period when defects are present in DNA.

- 0625 STUDY OF THE CARCINOGENICITY OF PRODUCTS FROM PHOTOINDUCED OXIDATION OF BENZO(a)-PYRENE. (Rus.) Gubergrits, M. Ia. (Inst. Exp. Clin. Oncol., Moscow, USSR), A. B. Linnik, L. P. Paal'me and L. M. Shabad. *Vopr Onkol* 20(1):77-81, 1974.

Benzo(a)pyrene (BP) was oxidized in benzene, acetone, ethanol and octane solutions by exposing 1×10^{-3} g/ml BP to light from a mercury-quartz lamp (maximum wavelength 365 nm at an intensity of 10^{16} quanta/ml/sec). The main products of photooxidation were identified as (1) a mixture of BP quinones (substituted in the 1,6 or 3,6 positions), (2) an oxidized BP derivative with an unknown structure, (3) 6-methyl BP (in acetone solutions only), and (4) unidentified high-molecular weight compounds resulting from polymerization and condensation of BP. After photooxidation the BP solutions were evaporated to dryness, dissolved in olive oil, and given (route unspecified) to 8-wk-old F_1 hybrid mice (C57Bl x CBA); controls

received 2 mg BP. Within 1 yr after treatment 5-37% of the mice given photooxidation products of BP developed sarcomas at the site of administration, while 80.65% of those given 2 mg BP developed sarcomas. The percentage of mice developing sarcomas was directly related to the quantity of unreacted BP left in the solution. These findings show that BP is carcinogenic while its photooxidation products are not. It is suggested that photooxidation of BP would be an effective method for reducing environmental pollution caused by polycyclic aromatic hydrocarbons.

- 0626 NEUROTROPIC EFFECT OF 7,12-DIMETHYLBENZ(a)-ANTHRACENE IN TRANSPLACENTAL CARCINOGENESIS. (E.) Napalkov, N. P. (Cancer Unit, World Health Org., Geneva, Switzerland) and V. A. Alexandrov. *J Natl Cancer Inst* 52(4):1365-1366, 1974.

On the 21st day after conception, pregnant random bred albino rats were given a single i.v. injection of an aqueous-lipid emulsion of 7,12-dimethylbenz(a)-anthracene (DMBA) (15 mg/kg). Among 28 offspring surviving more than 6 months, 21 developed tumors. In 14 of the tumor-bearing animals, the tumors were neurogenic; histologically, most of these were diagnosed as malignant neurinomas. There were also 8 kidney neoplasms (6 adenomas, 1 hypernephroid carcinoma, and 1 papillary adenoma) and 7 solitary tumors of various other sites. Seven of the 11 mothers which died also had neoplasms, none of which were neurogenic. These data suggest that, in transplacental carcinogenesis, a tropism could occur which is not inherent in the effect of a given carcinogen in postnatal life.

- 0627 A TRANSPLANTABLE ERYTHROBLASTIC STEM-CELL LEUKEMIA. (E.) Wise, W. C. (Dept. Physiol., Med. U. South Carolina, Charleston). *J Natl Cancer Inst* 52(2):611-612, 1974.

A lipid emulsion containing 7,8,12-trimethylbenz(a)-anthracene (TMBA) was injected into the caudal veins of Long-Evans rats five times at 14-day intervals, starting at 25-50 days. The livers of these animals, all of which developed an hepatic erythroblastic stem-cell leukemia (EBL), were excised and cell suspensions prepared. The cell suspension was injected i.p. into 1-5-day-old rat pups. The pups lived about 18.33 ± 7.98 days longer and all showed marked hepatomegaly. The transplanted leukemia showed a transmission rate of greater than 98%. These EBL cells should become a useful system for the study of cellular maturation and neoplastic transformation.

- 0628 THE ASSOCIATION OF NEOPLASTIC DISEASES AND MYCOTOXINS IN THE ENVIRONMENT. (E.) Aleksandrowicz, J. (Med. Acad., Cracow, Poland) and B. Smyk. *Tex Rep Biol Med* 31(4):715-726, 1973.

The fungal flora were examined in 210 human dwellings of patients with clinical tumor disease and 170 dwellings of clinically healthy persons. *Penicillium meleagrinum* was the species most often encountered in the dwellings of patients, followed by *Aspergillus*

flavus, *Cladosporium herbarum*, *Rhizopus nigricans* and *Alternaria geophila*. The most frequently found species in homes of patients with tumors were *Penicillium meleagrimum* and, slightly less often, *Aspergillus flavus*. Mycoflora in dwellings of married couples in which both partners suffered from tumors simultaneously or at intervals of 1-2 yr, showed *Aspergillus flavus* in 8 of 9 dwellings, compared with 2 of 9 control dwellings. *Penicillium meleagrimum* and *Cladosporium herbarum* were also relatively frequent in this group. In homes of cancer patients, *Aspergillus flavus* and *Penicillium meleagrimum* predominated. In dwellings of leukemia patients, *Penicillium meleagrimum* was most frequent, followed by *Aspergillus flavus* and *Cladosporium herbarum* and *Rhizopus nigricans*. These results indicate the presence of a higher incidence of fungi-producing oncogenic mycotoxins in the home environment of tumor patients.

0629 EFFECT OF AGE ON TUMOR INDUCTION IN C57BL MICE. (E.) Franks, L. M. (Imp. Cancer Res. Fund, Dept. Cellular Path., London, England) and A. W. Carbonell. *J Natl Cancer Inst* 52(2):565-566, 1974.

A single s.c. dose of 3-methylcholanthrene (MCA) (200 µg) was administered to weanling, adult, and aged C57BL/1crf mice of both sexes. Among the 21 aged mice, four died within the first 6 weeks and the remaining 17 developed s.c. tumors at the site of inoculation. Two lung adenomas, one carcinoma of the jejunum, three hepatomas, and four reticulo-endothelial sarcomas were also found among six mice. Of the 30 adult animals, 29 developed s.c. tumors, and 75% of the weanling mice developed tumors. The mean induction period was significantly longer among the weanling mice than among the aged mice. The tumors were structurally similar in all groups and there were no significant changes in the livers or kidneys. It is possible that the enzyme systems necessary for the metabolism which activates the MCA appear at about 2-3 weeks, accounting for the longer induction period in the younger animals. The results suggest that the pathway to tumor production by MCA in the s.c. tissues may differ from that following in spontaneous tumor formation.

0630 MUTAGENICITY OF DERIVATIVES OF THE ONCOGENIC PURINE N-OXIDES. (E.) McCuen, R. W. (Mem. Sloan Kettering Cancer Ctr., New York, N.Y.), G. Stöhrer and F. M. Sirotnak. *Cancer Res* 34(2):378-384, 1974.

The mutagenic activity of a group of activated purine N-oxides was studied. The N-acetoxy derivative, a chemical model of the reactive sulfate ester formed *in vivo*, inactivated and induced mutations in *Bacillus subtilis*-transforming DNA. There was reasonable correlation between the mutagenicity of the various acetoxy esters and the oncogenicity of the parent N-oxide derivatives. The acetoxy esters of 3-hydroxyxanthine and 3-hydroxy-1-methylguanine (both strong oncogens in rats) were the most potent mutagens. The acetoxy ester of 7-hydroxyxanthine was also a

strong mutagen. Acetoxy esters of the 7-methyl- and 8-aza-substituted 3-hydroxyxanthine derivatives, as well as 1-acetoxyadenine, 3-acetoxypurine, and 3-acetoxyhypoxanthine, were weak or not mutagenic at all. Most of the 3-acetoxyxanthine-induced mutations reverted spontaneously to wild type. Reversion frequency was increased to the greatest extent with ethylmethane sulfonate, but was also increased with the base analogs 2-aminopurine and 5-bromodeoxyuridine. Only a few of the mutations were reverted by frame-shift mutagens. It was concluded that mutation induction in transforming DNA by the acetoxy esters of purine N-oxides occurs by both transition and transversion base-pair substitution.

0631 TUMORS OF THE ESOPHAGUS AND DUODENUM INDUCED IN MICE BY ORAL ADMINISTRATION OF N-ETHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Nakamura, T. (Second Dept. Path., Nagoya City U. Med. Sch., Japan), M. Matsuyama and H. Kishimoto. *J Natl Cancer Inst* 52(2):519-522, 1974.

N-Ethyl-N'-nitro-N-nitrosoguanidine (ENNG) was administered to male and female CBA/H-T6 mice via the drinking water (50 mg ENNG/liter) for 10 months. Twenty-three animals died during the 10-month treatment period. Many of the remaining 43 animals developed tumors of the esophagus and duodenum, and a few developed gastric tumors. The control mice developed only spontaneous hepatomas. Sex did not affect tumor incidence. The esophageal tumors were multiple, of two sizes, and were diagnosed as papillomas and squamous cell carcinomas. Seven of the latter invaded the thyroid or mediastinal tissues. Most of the duodenal tumors were single and were histologically diagnosed as adenocarcinomas or hemangioendothelial sarcomas. Two-thirds of the former invaded the pancreas. The forestomach tumors were huge and malignant, metastasizing into the regional lymph nodes, pancreas, and liver. Tumors of the lung and liver were scarce among the treated mice, in which leukemia and hemangioendothelial sarcoma of the liver were occasionally found.

0632 SPECIFICITY OF CHEMICAL MODIFICATION OF RIBONUCLEIC ACID TRANSPORT BY LIVER CARCINOGENS IN THE RAT. (E.) Shearer, R. W. (Dept. Molecular Biol., Pacific Northwest Res. Fdn., Seattle, Wash.). *Biochemistry* 13(8):1764-1767, 1974.

Using male Buffalo rats, carcinogens and other drugs toxic to the rat liver were tested for their effects on the cellular mechanism which selects only a fraction of the RNA base sequence transcribed from transport to the cytoplasm. Cytoplasmic RNAs transcribed from families of related genes were compared by RNA-DNA hybridization in the presence of competing RNA. A single dose of any of five liver carcinogens (3'-methyl-4-dimethylaminoazobenzene, N-2-fluorenylaceta-mide, thioacetamide, aflatoxin B₁, and dimethylnitrosamine) caused the appearance in the cytoplasm of RNAs which are normally restricted to the nucleus. The defect occurred in a detectable number of cells within 2 hours and was not repaired 2 months later. No such defect occurred in adult rats after the administration of ethanol, urethane, or α-naphthyl iso-

thiocyanate, although dimethyl sulfoxide produced the same effect as the carcinogens. These results indicate the significance of gene regulation at the levels of transport of RNA from the cell nucleus to the cytoplasm.

0633 FORMATION OF DIMETHYLNITROSAMINE FROM DIMETHYLAMINE AND TRIMETHYLAMINE AT ELE-VATED TEMPERATURES. (E.) Scanlan, R. A. (Dept. Food Sci. Technol., Oregon State U., Corvallis), S. M. Lohsen, D. D. Bills and L. M. Libbey. *J Agr Food Chem* 22(1):149-151, 1974.

Varying concentrations of dimethylamine (DMA) and trimethylamine (TMA) were reacted with sodium nitrite at pH 6.4, 100 C, for 2.5 hr. In the presence of equimolar concentrations of amines and nitrite, more dimethylnitrosamine (DMNA) was produced from DMA rather than TMA. When the molar ratio of amine to nitrite was increased, the amounts of DMNA from the 2 amines became nearly equal, and, at very high amine to nitrite ratios, more DMNA was formed from TMA than from an equimolar amount of DMA. The optimum pH for the conversion of TMA to DMNA at 100 C was 3.2-3.3. These results indicate that, as the TMA to nitrite ratio increased, a different reaction mechanism became operative. The tertiary amine undergoes nitrosative dealkylation to the corresponding secondary amine which reacts with nitrite to form the N-nitrosamine. It is suggested that the catalytic effect of formaldehyde produced by nitrosative dealkylation of TMA explains the increased yields of DMNA at the higher TMA levels used in this study. Because relatively large amounts of TMA can form in refrigerated seafood, the dietary intake of TMA may have to be reevaluated if *in vivo* formation of DMNA from TMA does occur.

0634 EMBRYONAL CARCINOMAS IN SYRIAN HAMSTERS AFTER INTRATESTICULAR INOCULATION OF ZINC CHLORIDE DURING SEASONAL TESTICULAR GROWTH. (E.) Guthrie, J. (Southampton Gen. Hosp., England) and O. A. Guthrie. *Cancer Res* 34(10):2612-2614, 1974.

Zinc chloride solution (0.05 ml) injected into the testes of 49 Syrian hamsters during the early spring months resulted in two embryonal carcinomas of the testis found at necropsy ten wk later. The zinc chloride injections were made during the period of rapid seasonal gonadal growth when spermatogonial division is activated and resulted in areas of coagulative necrosis occupying about 25% of each testis. The tumor arose adjacent to the areas of necrosis.

0635 TUMOR-PROMOTING CROTON OIL FACTOR TETRA-DECANOYL-PHORBOL-ACETATE STIMULATES THY-MIDINE INCORPORATION INTO NORMAL AND CON A STIMULATED LYMPHOCYTES. (E.) Süß, R. (Inst. Exp. Pathol., Heidelberg, Germany) and A. Schuster. *Experientia* 30(1):81, 1974.

The incorporation of ³H-thymidine into normal and

Con A stimulated mouse spleen cells treated with tetradecanoyl-phorbol-acetate (TPA) was studied. TPA stimulated thymidine incorporation into the spleen cells after 72 hours incubation. This stimulation was only about 1/10 that obtained with Con A, if compared at maximal stimulating concentrations. No potentiating effect was observed when the lymphocytes were incubated simultaneously with TPA and Con A, although the stimulation was significantly enhanced when the cells were preincubated for 12 hours with Con A alone. Lymphocytes preincubated with TPA alone were less stimulated in the presence of Con A and TPA. The data support the hypothesis that TPA induces membrane changes. These membrane changes may imply the "masking" of Con A binding sites.

0636 VITAMIN A DEFICIENCY ENHANCES BINDING OF BENZO(a)PYRENE TO TRACHEAL EPITHELIAL DNA. (E.) Genta, V. M. (Nat'l. Cancer Inst., Bethesda, Md.), D. G. Kaufman, C. C. Harris, J. M. Smith, M. B. Sporn and U. Saffiotti. *Nature* 247(5435):48-49, 1974.

The tracheas of vitamin A deficient and control hamsters were incubated in L-15 medium containing ³H-benzo(a)pyrene (³HBP) under conditions which preserved biochemical function and morphology. Purified DNA isolated from the tracheal epithelial cells was banded in CsCl gradients. Substantially greater quantities of radioactivity were associated with the DNA prepared from the vitamin A deficient tracheas. When isolated tracheas were incubated in the presence of ³H-BP and equimolar amounts of 7,8-benzflavone (7,8-BF), an inhibitor of the aryl hydrocarbon hydroxylase system, the binding of ³H-BP to DNA was reduced. This suggests that the extent of BP binding to DNA depends largely on the ability of the tracheal epithelial cells to metabolize it. Determination of the extent of binding of benzo(a)pyrene to DNA during the short term organ culture of isolated tracheas may be applicable as a method for screening potential states (or individuals) with increased susceptibility to respiratory carcinogenesis.

0637 EFFECT OF BETA-OXIDIZED NITROSAMINES ON SYRIAN GOLDEN HAMSTERS. I. 2-HYDROXYPROPYL-N-PROPYLNITROSAMINE. (E.) Pour, P. (U. Nebraska Med. Ctr., Omaha), F. W. Krüger, J. Althoff, A. Cardesa and U. Mohr. *J Nat'l Cancer Inst* 52(4):1245-1249, 1974.

Male and female randombred Syrian golden hamsters were injected s.c. with 0.1, 0.05, or 0.025 of the LD₅₀ (1500 mg/kg) dose of 2-hydroxypropyl-n-propyl-nitrosamine (2-HPPN) once weekly for life. Most of the hamsters developed tumors of the nasal cavities (33-69%), laryngotracheobronchial tract (33-54%), or liver (7-40%). In addition, some animals developed tumors of the pancreatic duct, mesentery, hardierian gland, or parathyroid. Although the highest incidence of tumors was in the highest dose group, a dose-response relationship was not established for latency, incidence, or multiplicity of tumors; these parameters did not vary with sex. The carcinogenic effects of equitoxic doses of di-n-propylnitrosamine

(DPN) and methyl-n-propylnitrosamine (MPN) are more marked than those of 2-HPPN. Although all three compounds primarily affect the respiratory tract, the incidence and multiplicity of tumors induced varies from compound to compound. In addition, DPN does not induce liver tumors, while MPN and 2-HPPN do. On the basis of these results, the metabolic pathway of DPN carcinogenesis cannot be explained.

- 0638 DIETARY FACTORS WHICH MODIFY AFLATOXIN TOXICITY IN THE RAT. (E.) Wells, P. A. (U. California, Los Angeles). *Diss Abstr Int* 34 (11):5538-B, 1974.

Male weanling rats were maintained on diets containing 1.7 ppm aflatoxin and: no fat; saturated fat; polyunsaturated fat; or polyunsaturated fat in conjunction with low, normal, or high levels of dietary protein. Aflatoxin inhibited growth in all groups except those maintained on low protein diets. Liver size varied as a function of the severity of liver tumors and was most increased in animals on normal and high-protein diets. The aflatoxin-induced increase in liver size was small in animals maintained on saturated fat diets. Liver size was not increased in rats fed low protein diets or low protein diets supplemented with cystine. Liver cholesterol levels were increased in all animals except those fed low protein diets. The elevation was greatest among those fed saturated fat; sterculic acid markedly diminished the elevation in this group. Aflatoxin-induced elevations in plasma cholesterol were seen only in rats fed saturated fat diets, sterculic acid diminished this effect. In the sterol ester and triglyceride fractions of the plasma, the C18:2/C20:4 ratio increased with a decrease in the incidence and severity of tumors. C16:0 and C18:0 decreased and C18:1 increased in the liver sterol fraction in response to aflatoxin, except in the low protein group. Aflatoxin did not produce changes in the liver triglyceride fraction, which was, however, altered in the low protein group. C18:0 was decreased and C18:1 increased in the liver phospholipid fraction in response to aflatoxin, except in the low protein group. Thus, low protein diets, and to a lesser extent saturated fat-containing diets, protect against aflatoxin toxicity.

- 0639 GROWTH OF TRANSPLANTED AND INDUCED TUMORS IN RATS UNDER A SCHEDULE OF PUNISHED BEHAVIOR. (E.) Ray, P. (Howard U. Coll. Med., Washington, D. C.) and S. N. Pradhan. *J Natl Cancer Inst* 52(2):575-577, 1974.

Sprague-Dawley rats with transplanted 4M mammary carcinoma (0.2 ml saline suspension of minced tumor injected s.c.) or tumors induced by 7,12-dimethylbenz(a)anthracene (20 mg by intragastric instillation) were placed on a schedule of punished (conflict) behavior in which food reinforcement was paired with mild electric shock. This behavioral stress inhibited growth and development of both the transplanted and induced tumors. The role of neuroendocrine factors in stress-induced alteration in tumor growth is discussed. Behavioral stress with psychosomatic

involvement may alter homeostatic functions mediated through neuroendocrine mechanisms and cause hormonal imbalance. Such imbalance may be characteristic of the stage of resistance (adaptive) or the stage of exhaustion (maladaptive) of the General Adaptation Syndrome of Seyle. Inhibition of tumor growth in this study appeared indicative of the stage of resistance.

- 0640 NEOPLASMS AND AMYLOIDOSIS IN STRAINS OF MICE TREATED WITH 3-METHYLCHOLANTHRENE. (E.) Akamatsu, Y. (Med. Coll. Georgia, Augusta) and B. P. Barton. *J Natl Cancer Inst* 52(2):377-385, 1974.

Both sexes of five inbred strains of mice-BTOs, BALB/cOs, C57BL/6Os, C3HeB/0s, and C3H/HeOs-were given by gavage 1 mg 3-methylcholanthrene (MCA) in olive oil to compare their susceptibility to MCA carcinogenesis. Tumors occurring among these strains given MCA were classified as local, e.g., tumors of the skin and forestomach, or visceral, e.g., hepatomas, pulmonary adenomas, and lymphomas. Untreated BTOs and C3H/HeOs females had a high incidence of spontaneous mammary tumors. MCA-treated BTOs mice, particularly males, had the highest incidence of gastric tumors (67%), with squamous cell carcinoma of the forestomach comprising 26%. C3HeB/0s male mice treated with MCA also had a moderately high incidence of these gastric lesions (34%), with squamous cell carcinoma of the forestomach comprising 4%. The other strains developed only squamous papillomas after MCA treatment. The BALB/cOs strain was the most sensitive to visceral tumor formation after MCA treatment; pulmonary adenomas developed in 50% of the males and 62% of the females, and lymphomas developed in 20% of the males and 31% of the females. MCA-treated females of the C3H/HeOs, BALB/cOs, and C57BL/6Os strains developed amyloidosis more often than females. This amyloid was similar in morphology, histochemistry, and ultrastructure to that reported for human as well as experimental amyloid. In BTOs and C57BL/6Os males, the incidence of amyloidosis was significantly correlated with that of gastric neoplasms but not with that of any other type of neoplasm. Since C57BL/6Os and BTOs mice are genetically related, genetic factors could be involved in this association of amyloidosis and gastric neoplasia.

- 0641 BINDING OF CHEMICAL CARCINOGENS IN THE LUNG. (E.) Toft, D. O. (Mayo Clin., Rochester, Minn.) and T. C. Spelsberg. *J Natl Cancer Inst* 52(4):1351-1354, 1974.

The binding of tritium-labeled 3-methylcholanthrene (³H-MCA, 3.1 Ci/mole) was examined in the cytosol fraction from Charles River rat tissues. With sucrose gradient centrifugation, macromolecular complexes of ³H-MCA were observed in several tissues. A unique binding component was identified in the lung cytosol; other tissues produced a 4S component believed to be at least partially a result of contamination by serum proteins. The lung-binding component had a sedimentation coefficient of about 7S

under low ionic conditions. It was altered to a 5S form in the presence of 0.3M KCl, which suggested a subunit composition. The lung component was not found in other tissues tested (serum, liver, heart, kidney, testes, and uterus). These findings were verified by the *in vivo* administration of ^3H -MCA (500 μCi i.p.). Although the carcinogen was readily taken up by several tissues, only the lung contained a complex sedimenting in the 7S region of sucrose gradients. Binding specificity has not yet been described, but one other chemical carcinogen dibenz-(a,h)anthracene, was also bound by the lung component.

0642 HORMONE-DEPENDENT STEM-CELL RAT LEUKEMIA EVOKED BY A SERIES OF FEEDINGS OF 7,12-DIMETHYLBENZ(a)ANTHRACENE. (E.) Huggins, C. B. (Ben May Lab. Cancer Res., U. Chicago, Ill.), H. Yoshida and C. C. Bird. *J Natl Cancer Inst* 52(4): 1301-1305, 1974.

Mammary cancer and leukemia developed frequently in juvenile Long-Evans rats given multiple feedings of a lipid solution of 7,12-dimethylbenz(a)anthracene (DMBA) by gastric tube intubation. The first feeding consisted of 200 mg/kg DMBA and the seven subsequent biweekly feedings of 10 mg. The incidence was: mammary cancer, males 20% and females 66%; leukemia, males 70% and females 82%. Histological study of 56 consecutive leukemias induced by DMBA revealed 55 stem-cell leukemias and 1 myelogenous leukemia. The stem-cell leukemias grew exuberantly in sinusoids of liver, with diffuse replacement of the entire sinusoidal endothelium by leukemic stem cells. Allogenic transplantation of whole blood of rats with advanced stem-cell leukemia to the s.c. tissue of the newborn resulted in sarcomas composed of undifferentiated stem cells at the injection site, together with secondary leukemia. Many stem-cell sarcomas and leukemias regressed rapidly and completely after hypophysectomy. A difference between rat strains was found in the toxicity of DMBA. The LD₅₀ was 400 mg/kg for Long-Evans males and 235 mg/kg for Sprague-Dawley males. Multiple feedings of large amounts of DMBA to 12 Sprague-Dawley rats induced stem-cell leukemia in four of six surviving rats.

0643 OXIDATIVE METABOLISM OF NICOTINE BY CIGARETTE SMOKERS WITH CANCER OF THE URINARY BLADDER. (E.) Gorrod, J. W. (Inst. Psychiatry, London, England), P. Jenner, G. R. Keyse and B. R. Mikhael. *J Natl Cancer Inst* 52(5):1421-1424, 1974.

Nicotine and its major metabolites, cotinine and nicotine-1'-N-oxide, were measured in 24-hr urine collections from 21 normal healthy male cigarette smokers (aged 25-70 yr) and 23 cigarette smokers (aged 45-70 yr) with cancer of the urinary bladder. Analysis of replicate daily urine samples from some subjects showed the metabolite ratio cotinine/nicotine-1'-N-oxide to be an individual index of the alternate routes of oxidative metabolism of nicotine, despite variations in urine pH, volume, and daily nicotine intake. The ratio of cotinine to nicotine-

1'-N-oxide was significantly higher in cancer patients than in the control group. The implication of this finding in relation to the etiology of the disease and the metabolism of nicotine by alternate oxidative pathways is discussed. It is suggested that excretion of the nicotine metabolites may be a useful indicator of the development of urinary bladder cancer.

0644 TUMORIGENICITY OF METHYL-N-PROPYLNITROSAMINE IN SYRIAN GOLDEN HAMSTERS. (E.)

Pour, P. (U. Nebraska Med. Ctr., Omaha), F. W. Krüger, A. Cardesa, J. Althoff and U. Mohr. *J Natl Cancer Inst* 52(2):457-462, 1974.

Weekly s.c. injections (12.5, 25, and 50 mg/kg) of methyl-n-propylnitrosamine (MPN) given for life to Syrian golden hamsters caused tumors of the respiratory tract and liver. The main target tissue was the posterior region of the nasal cavity where adenocarcinomas and less-differentiated carcinomas were found in 88-95% of the hamsters. Papillomas were found in the larynx, trachea, and stem bronchi. Adenomas and carcinomas of the lung developed mainly in females treated with the highest dose. In the liver hemangioendotheliomas occurred at all dose levels, whereas the highest dose caused, in addition, cholangiomas and hepatocellular carcinomas. Differences in tumor sites do not allow the interpretation that MPN is a direct carcinogenic metabolite of di-n-propylnitrosamine. A methyl group in the aliphatic chain of nitrosamines might favor induction of neoplasms in the posterior part of the nasal cavity as well as development of liver tumors.

0645 EFFECTS OF ESTROGEN AND/OR PITUITARY GRAFT ON NUCLEIC ACID SYNTHESIS OF CARCINOGEN-INDUCED MAMMARY TUMORS IN RATS. (E.) Nagasawa, H. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan) and R. Yanai. *J Natl Cancer Inst* 52(4):1219-1222, 1974.

A study was made of the effects of estrogen and/or prolactin on the synthetic activity of DNA and RNA in mammary tumors of Sprague-Dawley rats induced by 7,12-dimethylbenz(a)anthracene (5 mg i.v.). Serum prolactin level was determined by radio-immunoassay. Ovariectomy resulted in a decrease of ^3H -thymidine incorporation into DNA and an increase in the ratio of ^{14}C -uridine incorporation into RNA: ^3H -thymidine into DNA ($^{14}\text{C}/^3\text{H}$ ratio). These changes returned to control levels, with an elevated serum prolactin level, following s.c. injection of 1 μg estradiol benzoate (EB) or isografts of two pituitaries; the effect was more marked with the former treatment than with the latter. Daily s.c. injection of 40 μg EB decreased ^3H -thymidine incorporation into DNA and increased the $^{14}\text{C}/^3\text{H}$ ratio. This decrease in ^3H -thymidine incorporation was ameliorated, with further marked increase in serum prolactin level, by simultaneous isografts of six pituitaries. The data indicate that, in nucleic acid synthesis, prolactin is of primary importance for the growth of carcinogen-induced mammary tumors. However, participation of estrogen in this process cannot be ruled out.

- 0646 DISTRIBUTION AND SOME PROPERTIES OF ACID PHOSPHATASE IN THE 7,12-DIMETHYLBENZ(a) ANTHRACENE-INDUCED RAT-MAMMARY CARCINOMA. (E.) Nicholson, R. I. (Tenovus Inst. Cancer Res., Welsh Natl. Sch. Med., Heath, Cardiff) and M. Davies. *Eur J Biochem* 44(1):25-35, 1974.

Differential centrifugation and gel-chromatography techniques were used to study the distribution and molecular forms of acid phosphatase in rat mammary tumors induced by 7,12-dimethylbenz(a)anthracene. With p-nitrophenylphosphate as substrate, three distinct forms of acid phosphatase activity were separated by gel chromatography. Enzyme I ($M_r > 200,000$) and enzyme II ($M_r 120,000$) had similar biochemical properties and differential centrifugation indicated that both enzymes are present in a sedimentable fraction. Disruption of a mitochondrial-lysosomal fraction by freezing and thawing released 45% of the total acid phosphatase of the fraction into a soluble phase. Treatment with detergent solubilized the bound enzyme. Two forms of acid phosphatase, one bound and one freely soluble, may exist in the lysosomes of rat mammary tumors. Enzyme III ($M_r 30,000$) was localized in the soluble fraction of the tumor cell and was biochemically distinct from enzymes I and II. Enzyme III may be assumed to be of the phosphoprotein phosphatase type of phosphohydrolases.

- 0647 CHRONIC EXPOSURE TO BENZENE AS A POSSIBLE CONTRIBUTORY ETIOLOGIC FACTOR IN HODGKIN'S DISEASE. (E.) Aksoy, M. (Internal Clin. Istanbul Med. Sch., Capa, Turkey), S. Erdem, K. Dincol, T. Hepyüksel and G. Dincol. *Blut* 28(4):293-298, 1974.

Of 94 Hodgkin's disease patients admitted to an Istanbul hospital between 1968 and 1972, six were workers who had been chronically exposed to benzene in concentrations of 150-210 ppm or more. The period of exposure ranged from 1-28 years, with an average of 11 years. The case histories of these six patients are briefly presented. These cases coupled with earlier findings indicate a possible etiological relationship between Hodgkin's disease and chronic benzene exposure.

- 0648 CARCINOGENESIS AND CHRONIC TOXICITY OF NITRILOTRIACETIC ACID IN SWISS MICE. (E.) Greenblatt, M. (U. Otago Sch. Med., Dunedin, New Zealand) and W. Lijinsky. *J Natl Cancer Inst* 52(4):1123-1125, 1974.

Swiss mice were treated p.o. for 26 wk with 5 g nitrilotriacetic acid (NTA)/liter, 5 g NTA plus 1 g NaNO_2 /liter, or 2 g N-nitrosoiminodiacetic acid (NIDA)/liter, and killed at 35-36 wk. Control animals received no treatment, 1 g NaNO_2 /liter, or 1.0 g N-nitrosopiperidine (NP)/liter as a positive control. Approximately 80 mice in each experimental group were divided equally by sex. Animals were studied mainly for induction of lung adenomas by the Shimkin screening method; other pathologic lesions were also evaluated by extensive light microscopy. NP-treated animals had 1.35-1.67 adenomas/mouse, a 10-fold increase in frequency compared with negative

controls. Comparison with untreated controls (sexes compared separately) showed no significant increase in the number of lung adenomas or lung-adenoma-bearing mice in any group. NIDA-treated animals of both sexes and males given NTA had significantly decreased numbers of adenomas compared with controls. The most common other tumor was the malignant lymphoma, which was predominant in females. No renal or osseous changes were detected by light microscopy. Other pathologic lesions were equally distributed in all experimental groups. NTA did not appear to be carcinogenic in Swiss mice in these tests.

- 0649 SUSCEPTIBILITY OF AN INBRED STRAIN OF GUINEA PIGS TO THE INDUCTION OF PANCREATIC ADENOCARCINOMA BY N-METHYL-N-NITROSOUREA. (E.) Reddy, J. K. (U. Kansas Med. Ctr., Kansas City), D. J. Svoboda and M. S. Rao. *J Natl Cancer Inst* 52(3):991-993, 1974.

Inbred NIH guinea pigs of both sexes were given N-methyl-N-nitrosourea (MNU) (10 mg/kg/week) by intragastric administration. Seven of 24 animals died during the initial stages of MNU administration due to acute hemorrhagic necrosis of the gastric mucosa, pulmonary hemorrhage, or pneumonia. Six additional animals died within 6 months because of severe atrophy of the exocrine pancreas and concomitant occurrence of marked fatty metamorphosis of the liver. One of the surviving males died after 28 weeks with a pancreatic tumor; another male died after 33 weeks with a pancreatic tumor. Laparotomy after 36 weeks revealed tumors with gross involvement of the pancreas in 2 females; one had metastatic nodules in the liver. Histologically, the tumors were moderately differentiated adenocarcinomas with marked desmoplastic reaction of the stroma. The metastatic nodules in the liver of the one female showed an adenocarcinomatous pattern. Although no tumors of the stomach or intestinal tract were observed, several foci of atypical hyperplasia were seen in the stomach mucosa. The inbred strain-13 guinea pigs may prove valuable in developing a suitable biologic model for pancreatic adenocarcinoma.

- 0650 EXPERIMENTAL STUDIES ON ASBESTOS CARCINOGENICITY. (E.) Shabad, L. M. (Inst. Exp. Clin. Oncol., Acad. Med. Sci., Moscow, USSR), L. N. Pylev, L. V. Krivosheeva, T. F. Kulagina and B. A. Nemenko. *J Natl Cancer Inst* 52(4):1175-1187, 1974.

The carcinogenic activity of different types of asbestos of the USSR was investigated. All chrysotile had traces of benzo(a)pyrene and high adsorption activity. BP was not found in anthophyllite and magnesiarfvedsonite. Three intratracheal injections of 2 mg chrysotile with 0.144 mg adsorbed BP induced tumors in 29% of 30 rats; the tumors included lung papillomas and reticulosarcomas but not carcinomas. A single intratracheal injection of 2 mg chrysotile + 5 mg BP induced lung carcinomas, lung papillomas, and sarcoma-like and papillary pleural mesotheliomas. Inhalation of 230 mg/m³ chrysotile induced lung and pleural precancerous lesions in 20% of 46 exposed rats. Addition of 1 mg BP or tobacco smoke increased

the frequency of these lesions to 57 and 38%, resp. Intrapleural administration of chrysotile (20 mg injected 3 times) induced mesotheliomas in 46% of treated rats. Histologically, the pleural mesotheliomas were sarcoma-like "mesenchymatous", adenomatous, and mixed. A transplantable mesothelioma is in its 26th generation.

0651 SMOKING AND CANCER. (E.) Burch, P.
(Dept. Med. Physics, U. Leeds, Great Britain). *New Scientist* 61(891):837, 1974.

It is hypothesized that the different classes of smokers are associated (but not on a single one-to-one basis) with distinctive genotypes and that these, in turn, are positively associated to different degrees with the genotypes that predispose to lung cancer. Various studies have revealed significant anthropometric differences between smokers and non-smokers as well as between cigar and pipe smokers. However, this theory does not deny a role for environmental factors (e.g., smoking) in the development of lung cancer.

0652 PERSISTANCE OF O6-ETHYLGUANINE IN RAT-BRAIN DNA: CORRELATION WITH NERVOUS SYSTEM-SPECIFIC CARCINOGENESIS BY ETHYLNITROSOUREA. (E.) Goth, R. (Max-Planck-Inst. Virus Res., Tübingen, Germany) and M. F. Rajewsky. *Proc Natl Acad Sci USA* 71(3):639-643, 1974.

N-ethyl-N-nitrosoourea was administered to rats of the BD IX strain. Similar initial degrees of DNA ethylation were found in the DNA of the brain and of the liver, in terms of the molar fractions of O6-ethylguanine, N7-ethylguanine, and N3-ethyladenine 1 hr after a pulse of (1-¹⁴C)ethylnitrosoourea. However, over a 240 hr period, the elimination rate from DNA of O6-ethylguanine (a modified base likely to cause anomalous base pairing during DNA replication) was strikingly slower in the brain, half-life about 220 hr, as compared to the liver, half-life about 30 hr, and also much slower than the elimination rates from brain DNA of N7-ethylguanine, about 90 hr, and N3-ethyladenine, about 16 hr. This apparent insufficiency of the brain cells to eliminate O6-ethylguanine from DNA might be a determinant in the nervous system-specific neoplastic transformation by N-ethyl-N-nitrosoourea, perhaps by enhancing the probability of the fixation of structural alterations in DNA during subsequent replication.

0653 THE TUMOR-PROMOTER PHORBOL ESTER (12-O-TETRADECANOYL-PHORBOL-13-ACETATE), A POTENT AGGREGATING AGENT FOR BLOOD PLATELETS. (E.) Zucker, M. B. (New York U. Sch. Med., New York), W. Troll and S. Belman. *J Cell Biol* 60:325-336, 1974.

The phorbol ester 12-O-tetradecanoyl-phorbol-13-acetate, a potent tumor-promoting agent, caused irreversible platelet aggregation when more than 0.02 μ M was stirred with human citrated or heparinized platelet-rich plasma (PRP) or when 1 nM was mixed

with washed platelets. The alcohol phorbol, which has little tumor-promoting activity, failed to cause platelet aggregation. With all but low concentrations of phorbol ester, aggregation was succeeded by a rapid phase, which was prevented or reduced by aspirin and enzymes which destroy ADP, was associated with a change in platelet shape, and was presumably due to released ADP. At higher concentrations, only a rapid phase was seen, and these inhibitors were ineffective. Low concentrations did not aggregate platelets in PRP containing sufficient EDTA or EGTA to chelate ionized calcium or in PRP from thrombathenic patients, higher concentrations caused slight aggregation. Both the primary, non-ADP-dependent aggregation and the rapid ADP-dependent aggregation were markedly inhibited by substances which increase cyclic AMP, metabolic inhibitors, and the sulphydryl inhibitor N-ethylmaleimide. Phorbol ester reduced platelet cyclic AMP only when it had been previously elevated by prostaglandin E₁. One μ M did not release β -glucuronidase, lactic dehydrogenase, or inflammatory material from platelets in 4-5 minutes, despite marked aggregation; all three were liberated within 30 minutes. The data suggest that the primary aggregating effect of phorbol ester is mediated by platelet actomyosin.

0654 A NEW ROUTE TO 3a,8a-DIHYDROFURO(2,3-b)BENZOFURANS. (E.) Pawlowski, N. E. (Dept. Food Sci. Technol., Oregon St. U., Corvallis), D. J. Jones and R. O. Sinnhuber. *Tetrahedron Lett* (14): 1321-1323, 1974.

The alkylation of phenol in glyme with 3-bromo-1,5-hexadiene in the presence of potassium carbonate yields a primary ether (3) containing less than 1% of its secondary isomer. The borontrichloride catalyzed Claisen rearrangement of the cold ether 3 leads to O-(3-hexa-1,5-dienyl)phenol (4), in 49% yield. The only side product from the rearrangement is the ether cleavage product, phenol. Oxidative cleavage of the two double bonds in 4 with osmium tetroxide-sodium periodate yields a hemiacetal (6, R=OH), which is easily converted to its more stable acetate (7, R=COCH₃). Pyrolysis of 7 yields 3a,8a-dihydrofuro-(2,3-b)benzofurans, which are intermediates in the formation of aflatoxin B₁.

0655 ENZYMIC REDUCTION OF CARCINOGENIC AROMATIC NITRO COMPOUNDS BY RAT AND MOUSE LIVER FRACTIONS. (E.) Poirier, L. A. (Natl. Cancer Inst., Bethesda, Md.) and J. H. Weisberger. *Biochem Pharmacol* 23(3):661-669, 1974.

The enzymatic reduction of 2-nitronaphthalene and similar aromatic nitro compounds by rat liver extracts was investigated. The incubation of 2-nitronaphthalene with the post-mitochondrial fraction of rat and mouse liver led to the slow formation of 2-naphthylamine and to the disappearance of 2-nitronaphthalene; the reaction also occurred with the cytoplasmic and microsomal fractions of rat liver and was generally accelerated by NADPH and FMN. No 2-naphthylhydroxylamine was observed at any time during the reduction, even with the use of gas-liquid

chromatographic system capable of detecting 5 μ g of 2-naphthylhydroxylamine added to the incubation mixture. The similar incubation of 2-nitrobiphenyl and 1-nitronaphthalene also led to the slow formation of the corresponding arylamine, with no evidence of hydroxylamine accumulation. 2-Naphthylamine was also produced both chemically and enzymatically by incubating 2-naphthylhydroxylamine with rat liver post-mitochondrial supernatant. In contrast to 2-nitronaphthalene, 4-nitroquinoline-N-oxide was rapidly reduced by rat liver post-mitochondrial fraction to yield high levels of the 4-hydroxylamine derivative, as well as small but significant quantities of the corresponding amine. These results support the contention that the carcinogenic activities of aromatic nitro compounds may be attributed to their conversion *in vivo* to reactivate hydroxylamine intermediates.

0656 SPIN CONCENTRATION PER LIVING CELL OF NORMAL LIVER, REGENERATING LIVER, AND HEPATOMAS. (E.) Abe, H. (Dept. Pathophysiol., Cancer Res. Inst., Kanazawa U., Japan) and Y. Kurata. *Gann* 65(1):75-78, 1974.

The free radical content was measured in living cells prepared from normal rat liver, liver from animals fed 3'-methyl-4-(dimethylamino)azobenzene, regenerating liver following partial hepatectomy, and ascites hepatoma. The free radical concentration of the normal liver cells was approximately 2.02×10^{13} spins/ 10^5 cells. In the liver cells from the carcinogen fed animals, the free radical content decreased to 1/3 normal after 2 months, and to 1/4 to 1/5 normal after 5 months. The ascites hepatoma cells showed extremely weak free radical signals, the free radical concentration varying between 0.04×10^{13} spins/ 10^5 cells (ascites hepatoma AH-13) and about 0.08×10^{13} spins/ 10^5 cells. In the regenerating cells, the free radical concentration reached minimum values 3 to 5 days after radical concentration of partial hepatectomy and began to increase after 7 days. The free radical value in these cells 11 days after surgery was still lower than in the normal cells. The results suggest that the free radical concentration decreases as a function of decreasing cellular morphological differentiation. The marked decrease in free radicals in cancer cells might be attributed to qualitative changes in the mitochondria as well as to a change in the nature of the cell membrane or other subcellular organs.

0657 AN EVALUATION OF THE TUMORIGENICITY OF CYCLOPHOSPHAMIDE AND URETHAN IN NEWBORN MICE. (E.) Kelly, W. A. (Dept. Path. Toxicol., Mead Johnson Res. Ctr., Evansville, Ind.), L. W. Nelson, H. C. Hawkins and J. H. Weikel, Jr. *Toxicol Appl Pharmacol* 27(3):629-640, 1974.

Charles River CD-1 mice were treated i.p. with normal saline, cyclophosphamide (0.8, 4.0, or 20.0 mg/kg), or urethan (700.0 mg/kg) within 24 hours of birth and at 3 and 6 days of age. Cyclophosphamide was not leukemogenic during the 79-week experimental period. The incidence of malignant lymphoma was comparable for the control and low- and middle-dose groups, histolo-

gic evidence of this disease being totally absent from the high-dose cyclophosphamide group. Liver neoplasms did not occur in the low- and high-dose groups, and the frequencies in the middle-dose group and controls were similar. The frequency of pulmonary adenoma was slightly increased in the low- and middle-dose cyclophosphamide-treated animals and in the high-dose females; however, neoplastic and hyperplastic lesions were totally absent from the lungs of the high-dose males. A high percentage of the urethan-treated mice developed malignant lymphomas and the incidence of neoplasms and hyperplastic nodules in the lungs and liver was increased in the urethan-treated males. Thus, in contrast to urethan, cyclophosphamide has a comparatively weak promoting, enhancing, and accelerating effect on the appearance of neoplasms in CD-1 mice.

0658 INDUCTION OF MAMMARY GLAND AND SKIN TUMORS IN FEMALE RATS BY THE FEEDING OF BENZYL VIOLET 4B. (E.) Ikeda, Y. (Dept. Toxicol., Natl. Inst. Hyg. Sci., Tokyo, Japan), S. Horiuchi, A. Imoto, Y. Kodama, Y. Aida and K. Kobayashi. *Toxicology* 2(3): 275-284, 1974.

A group of 35 female Sprague-Dawley rats was fed a diet containing at first 1%, then 3% Benzyl Violet 4B for 1 week each, then maintained on a diet containing 5% of the chemical for 12 months. A second group of 35 rats served as controls. In the experimental group, growth was significantly depressed although food consumption was almost the same as that of the controls. Only 2 animals survived the entire experimental period. The first appearance of tumors was noted on the left lower abdomen at 13 weeks time. Tumors developed externally in 22 out of 35 animals which included 11 animals with mammary gland carcinoma, 4 with squamous cell carcinoma of the skin and 7 animals with both types of tumors. Though the majority of the squamous cell carcinomas developed in the ear-duct, they also appeared earlier than the squamous cell carcinomas of the skin. No external tumor was observed in the control group. The results of this study combined with those from similar studies leave little doubt that Benzyl Violet 4B is carcinogenic under the experimental conditions herein employed. The color was deleted from the food additives list in Japan in December, 1972, where it has been in wide use until that time.

0659 EFFECTS OF LEAD OXIDE ON THE INDUCTION OF LUNG TUMORS IN SYRIAN HAMSTERS. (E.) Kobayashi, N. (Am. Hlth. Fdn., New York, N.Y.) and T. Okamoto. *J Natl Cancer Inst* 52(5):1605-1610, 1974.

In 10 weekly intratracheal injections, three groups of Syrian golden hamsters were given a suspension (in isotonic saline plus 0.5% carboxymethylcellulose (CMC) solution) of lead oxide (PbO, 1 mg), benzo(a)pyrene (BP, 1 mg), or a mixture of PbO and BP (1 mg each). A fourth group received CMC-saline alone, while a fifth group served as untreated controls. Atypical epithelial proliferation, 11 adenomas, and an adenocarcinoma were observed in the lungs of hamsters given BP mixed with PbO, whereas no tumorous changes were

found in the other groups. These neoplastic changes originated mostly in the bronchiolo-alveolar area. PbO alone induced hyperplastic and squamous metaplastic foci of the alveolar area. The results suggest a cocarcinogenic effect of PbO.

0660 EFFECTS OF DIETARY FAT LEVEL AND DIMETHYLHYDRAZINE ON FECAL ACID AND NEUTRAL STEROL EXCRETION AND COLON CARCINOGENESIS IN RATS. (E.) Reddy, B. S. (American Hlth. Fdn., New York, N.Y.), J. H. Weisburger, and E. L. Wynder. *J Natl Cancer Inst* 52(2):507-511, 1974.

Studies were conducted on Fischer rats to determine the effect of dietary fat on the induction of colon tumors by 1,2-dimethylhydrazine (DMH, 10 mg/kg s.c. for 20 wk) and the effect of dietary fat and DMH on fecal excretion of acid and neutral sterols. High fat (20%) intake was associated with an increased fecal acid and neutral sterol excretion. Fecal acid sterols were more extensively degraded in rats fed a high-fat diet than in rats fed low-fat (0.5%) or normal-fat (5%) diets. DMH-treated animals excreted high levels of acid and neutral sterols and more microbially modified acid steroids than did controls. Animals fed high-fat diet and treated with DMH had a higher incidence of colon tumors and increased number of tumors/animal than did similarly treated rats on low-fat, normal-fat, or Purina Lab Chow diets. The colon tumors were adenocarcinomas invading the serosa and involving the regional lymph node.

0661 AN ELECTRON MICROSCOPE STUDY OF THE RESPONSE OF MESOTHELIAL CELLS TO THE INTRAPLEURAL INJECTION OF ASBESTOS DUST. (E.) Davis, J. M. G. (Inst. Occupational Med., Edinburgh, Scotland). *Br J Exp Pathol* 55(1):64-70, 1974.

Bernard Hartley Guinea pigs, Wistar rats, and Balb/C mice were injected intrapleurally with either crocidolite or chrysotile asbestos dust, the doses being 25 mg for the guinea pigs and rats and 10 mg for the mice. The mesothelial cells lining the pleural cavities of these animals were examined by light and electron microscopy at intervals from 7 days to 6 months after injection of the dust. The dusts did not induce mesothelial hyperplasia during this period. During this first few days after treatment, some areas of mesothelial cells became rounded and less clearly attached to one another, and a few contained small numbers of asbestos fibers. There was also evidence at this time of penetration of the asbestos fibers between the mesothelial cells into the submesothelial connective tissues. Later, the mesothelium covering most of the pleural cavity returned to normal; however, where mesothelium covered asbestos granulomas, the cells were extremely flattened and lacked surface microvilli. Usually the mesothelial covering was complete, but in some areas pores penetrated the mesothelial cell cytoplasm, leaving areas of connective tissue in direct contact with the pleural cavity. In a few cases, the mesothelial cells lined clefts within the connective tissue of the asbestos granulomas. The effects of the dusts did not vary significantly among the three species. The crocidolite

dust tended to spread more rapidly than the chrysotile dust after injection, and the crocidolite granulomas tended to be smaller, more numerous, and more widely scattered than the chrysotile granulomas.

0662 CARCINOGENESIS IN TISSUE CULTURE. 23: POPULATION ANALYSIS IN THE CULTURES OF TRANSFORMED RAT LIVER CELLS BY CELL ELECTROPHORESIS. (E.) Yamada, T. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan), T. Takaoka and H. Katsuta. *Japan J Exp Med* 44(2):199-210, 1974.

An automatic photo-recording cell electrophoresis apparatus was used in the population analysis of eight cultured strains of rat liver cells which had undergone spontaneous or chemically-induced (4-nitroquinoline-1-oxide (4NQO)) transformation. One half of each cell sample was treated with neuraminidase prior to electrophoresis. The mean mobilities of the eight lines ranged between 0.876 and 1.099 μ /sec/V/cm, with neuraminidase causing a 0.4% to 16.5% reduction in mobility. The mobility of the normal cell line RLC-10(2) was little affected by the neuraminidase treatment. The frequency of malignant transformation in each cell population was determined based on the following criteria: the number of individual cells showing mean mobilities at least 10% greater than those of the control samples; and the number of individual cells showing a neuraminidase-induced reduction in mobility at least 10% greater than that shown by the control samples. The frequency of malignant transformants before and after neuraminidase treatment varied among the eight cell lines. The neuraminidase-induced reductions in mobility did not vary greatly among the transformed cells of the various cultures. The greatest number of malignantly transformed cells anticipated by the electrophoretic criteria was found among the medium sized cells of each line. The data indicate that the number of malignant cells in a population varies according to the way in which the original culture was transformed.

0663 INTERCELLULAR IMMUNOFLOUORESCENCE IN CHEMICALLY INDUCED SQUAMOUS EPITHELIAL TUMORS OF MOUSE SKIN. (E.) Pertschuk, L. P. (Inst. Pathol., Kings County Hosp. Ctr., Brooklyn, N.Y.), K. Szabo and Y. Rosen. *J Invest Dermatol* 62(5):522-525, 1974.

Forty-five 9,10-dimethyl-1,2-benzanthracene (DMBA)-induced benign and malignant squamous cell tumors of the skin of C101 mice were examined by indirect immunofluorescence using sera from patients with active pemphigus vulgaris. All of these tumors showed positive intercellular fluorescence. In the 35 squamous papillomas, there was bright fluorescence outlining the squamous cells and none between the basal cells. A similar clear fluorescence was seen in the three *in situ* carcinomas and in two of the seven invasive squamous cell carcinomas. The other five invasive squamous cell tumors showed a varied picture, the overall effect being one of a lesser degree of fluorescence. No ICS was visible in two sarcomas, and no fluorescence was seen in any of the control tumor sections reacted with normal human serum.

These findings parallel observations in comparable lesions in man and other animals and suggest subtle antigenic changes in malignant squamous cells.

- 0664 SPECIES DEPENDENT TOXICITY OF SIX SUBSTITUTED HYDRAZINES. (E.) Shimizu, J. (Eppley Inst. Res. Cancer, U. Nebraska Med. Ctr., Omaha) and B. Toth. *Res Commun Chem Pathol Pharmacol* 7(4):671-678, 1974.

Randomly bred Swiss mice and Syrian hamsters received varying levels of the following chemicals daily in their drinking water: ethylhydrazine HCl (EH); n-allylhydrazine HCl (AH); 1-hydrozinophthalazine HCl (HPH); benzylhydrazine di HCl (BH); benzoylhydrazine (BOH); and 1,1-dimethylhydrazine (unsymmetrical) (1,1-DMH). The maximum tolerated doses of EH and AH were 0.025% for hamsters and 0.0125% for mice. The maximum tolerated dose of HPH was 0.5% for hamsters and 0.25% for mice. The maximum tolerated dose of BH was 0.125% for hamsters and 0.015625% for mice. The maximum tolerated dose of BOH was 0.08% for hamsters and 0.01% for mice. The maximum tolerated dose of 1,1-DMH was 0.1% for hamsters and 0.01% for mice. A possible difference in the metabolism of these compounds in the two species might account for the relative insensitivity of the hamster to their toxic effects.

- 0665 EVALUATION OF AN *IN VITRO* ASSAY SYSTEM FOR CARCINOGENS BASED ON PRIOR INFECTION OF RODENT CELLS WITH NONTRANSFORMING RNA TUMOR VIRUS. (E.) Rhim, J. S. (Microbiol. Assoc., Inc., Bethesda, Md.), D. K. Park, E. K. Weisburger and J. H. Weisburger. *J Natl Cancer Inst* 52(4):1167-1173, 1974.

Different types of chemical carcinogens (polycyclic hydrocarbons, azo dyes, aromatic amines, nitrosamines, and urethans) and some noncarcinogenic analogs were tested *in vitro* for their transforming activity in the AKR leukemia virus-infected NIH Swiss mouse embryo cell system. In each case, the *in vitro* carcinogenic activity was compared with the known *in vivo* carcinogenic activity of the chemical being tested. Of eight coded samples tested, the *in vitro* activity of seven agreed with the known *in vivo* activity, the exception being N-hydroxy-N-2-fluorenylacetamide, which did not induce transformation. The transforming activity of the polycyclic hydrocarbons, azo dyes, aromatic amines, nitrosamines, urethans, and miscellaneous chemicals generally correlated well with their reported carcinogenic activities. However, transformation was not induced by a known carcinogenic hydrocarbon (dibenz(a,c)anthracene) and one of the two carcinogenic azo dyes (3-methyl-4-dimethylaminoazobenzene). One aromatic amine (2-biphenylamine), inactive *in vivo*, was a transforming agent *in vitro*, a weak *in vivo* carcinogen (acetamide) was also active *in vitro*, and a known carcinogen (N-hydroxy-N-2-fluorenylacetamide) was twice negative *in vitro*. Phenanthrene gave variable results. Thus, the AKR virus-infected NIH Swiss mouse cell system is a reliable and reproducible system for the detection of chemical carcinogens.

- 0666 DETECTION OF METABOLIC CARCINOGEN INTERMEDIATES IN URINE OF CARCINOGEN-FED RATS BY MEANS OF BACTERIAL MUTAGENESIS. (E.) Commoner, B. (Ctr. Biol. Natural Systems, Washington U., St. Louis, Mo.), A. J. Vithayathil and J. I. Henry. *Nature* 249(5460):850-852, 1974.

Male Holtzman rats were maintained on normal diets or diets supplemented with 0.67 mg/g of 2-acetylaminofluorene (AAF) or 0.6 mg/g of p-dimethylaminoazobenzene (DAB). At varying intervals urine from these animals was tested for mutagenicity using a strain of histidine-negative *Salmonella typhimurium* (TA 1538). Urine samples obtained from the AAF-fed rats in successive weeks yielded progressively larger numbers of revertant, histidine-positive colonies, indicating the presence of intrinsically mutagenic substances in these urine samples. Incubation of the urine samples with a mixture of β -glucuronidase and Taka-diastase considerably increased the mutagenic activity of the samples. Thus part of both the inherently active intermediates and the carcinogen intermediates occur in the urine as glucuronides. Urine samples from the DAB-fed rats showed no mutagenic activity, although significant mutagenic activity was found following release of the active intermediates from their conjugated forms. Of a total of 45 μ g/ml of carcinogen-derived material in the samples derived from the AAF-fed animals, 2.2 μ g/ml was of urinary origin and represent both inherently active and activatable intermediates of AAF. All of the mutagenic activity in the urine of the DAB-fed rats is due to glucuronides of urinary origin.

- 0667 ANGIOSARCOMA OF THE LIVER IN A VINYL-CHLORIDE WORKER. (E.) Lee, F. I. (Dept. Med. Victoria Hosp., Blackpool, Great Britain) and D. S. Harry. *Lancet* 1(3870):1316-1318, 1974.

A 71-year-old man was admitted to the hospital with massive edema, moderate ascites, and a palpable liver. The spleen was also enlarged, serum bilirubin raised, serum albumin decreased, and prothrombin activity 35%. The liver architecture was normal and there was no evidence of hepatoma. The patient died suddenly 2 weeks later. Postmortem examination revealed angiosarcoma of the liver and several small sessile polyps on the mucosa of the fundus of the stomach. The spleen was enlarged due to portal hypertension and the other organs were normal. The patient has been a process worker in the manufacture of polyvinyl chloride from vinyl-chloride monomer for 20 years. There is strong evidence that angiosarcoma of the liver is an occupational tumor and that vinyl chloride is the carcinogen; there is no evidence that the finished polymer carries any risk.

- 0668 CARCINOGENIC ACTIVITY OF SMOKE CONDENSATE FROM CIGARETTES WITH AMMONIUM SULFAMATE-TREATED PAPER. (E.) Bock, F. G. (Roswell Pk. Mem. Inst., Buffalo, N.Y.), I. Michelson, I. D. J. Bross and R. L. Priore. *Cancer* 33(4):1010-1016, 1974.

The long-term tumorigenic activity of "conditioned"

cigarettes, the paper of which had been treated with varying amounts of ammonium sulfamate (AS), was studied. Heptane-soluble tar separated from the cigarette smoke condensates (CSC) of these and untreated, control cigarettes were applied to the dorsal skin of young ICR Swiss mice. The tars from the AS-treated cigarettes produced significantly fewer tumors than those from the controls during the early and middle stages of the experiment. However, during the later stages of the experiment (after the 54th week), these differences decreased, and by the end of the experiment (75 weeks) the tumor incidence in the two groups were not significantly different. The differences in the time course of tumor development indicate an approximately 1/3 reduction in co-carcinogen concentration in the AS-treated cigarettes. There was no significant difference in the effects of cigarettes treated with different levels of AS. Before ascertaining the significance of these results with regard to decreasing the hazard of cigarettes for humans, possible deleterious effects of AS-treated cigarettes must be evaluated.

0669 EARLY APPEARANCE OF "TRANSFORMED" CELLS FROM THE KIDNEYS OF RATS TREATED WITH A "SINGLE" CARCINOGENIC DOSE OF DIMETHYLNITROSAMINE (DMN) DETECTED BY CULTURE *IN VITRO*. (E.) Borland, R. (Baker Med. Res. Inst., Victoria, Australia) and G. C. Hard. *Eur J Cancer* 10:177-184, 1974.

Wistar rats were maintained on a sugar and water diet for 72 hours, then given a single i.p. injection of 60 mg dimethylnitrosamine (DMN). Monolayer cell cultures were established from cortical kidney tissue following removal of the rat kidneys 20 hours, 24 hours, 3 days, 5 days, or 7 days after DMN treatment. Cells isolated from the DMN-treated animals as early as 20 hours after treatment showed a prolonged lifespan *in vitro*, exhibited morphological transformation and an increased mitotic index, produced colonies in methylcellulose gels, showed a high relative plating and growth efficiency, and were agglutinated in the presence of Concanavalin A. No cytoagglutination was observed in the absence of Con A. These results indicated that the kidney cells from the DMN-treated rats were manifestly different from normal cells and that they had been transformed within the first 20 hours following DMN treatment.

0670 EFFECT OF SHORT-TERM ADMINISTRATION OF N-NITROSO COMPOUNDS ON LIVER HISTOLOGY AND ON PENTOBARBITAL-INDUCED SLEEPING TIME IN MICE. (E.) Nishie, K. (Richard B. Russell Agr. Res. Ctr., U.S. Dept. Agr., Athens, Ga.), W. P. Noreed and J. W. Pensabene. *Res Commun Chem Pathol Pharmacol* 8(2): 301-311, 1974.

Several nitrosamines and a few nitrosoureas were administered p.o. to male Swiss Webster mice on two successive days. On the third day, the duration of sleeping time in response to i.p. pentobarbital (80 mg/kg) administration (PST) was determined. All of the carcinogenic nitrosamines tested, except dipentyl nitrosamine, increased PST. These nitrosamines also caused a loss of glycogen, lipid accumu-

lation, swelling of hepatocytes or hemorrhage, and necrosis with lymphocytic infiltration in either the centrilobular or periportal areas of the liver. Dipentyl nitrosamine, which is a weak carcinogen, resembled the noncarcinogenic nitrosamines (dicyclohexylnitrosamine, N-ethyl-N-tert-butyl nitrosamine, N-nitrosopropylneethylester) in significantly reducing PST. Dipentyl nitrosamine also increased the smooth endoplasmic reticulum of the hepatocytes. The carcinogenic nitrosoureas did not produce visible histological changes in the liver. 1-Butyl-1-nitrosourea and dimethylnitrosourea increased PST, while 1-methyl-1-nitrosourea and 1-ethyl-1-nitrosourea shortened it. The differential hepatotoxicity of nitrosamines may be a useful indicator of the carcinogenic nature of these compounds.

0671 PROLACTIN STIMULATION OF ESTROGEN RECEPTOR *IN VITRO* IN 7,12-DIMETHYLBENZ(a)ANTHRACENE-INDUCED MAMMARY TUMOR. (E.) Sasaki, G. H. (U. Oregon Med. Sch., Portland) and B. S. Leung. *Res Commun Chem Pathol Pharmacol* 8(2):409-412, 1974.

Tumors were induced in female Sprague-Dawley rats by the intragastric feeding of 16 mg 7,12-dimethylbenz(a)anthracene (DMBA). The animals were then ovariectomized (OVX) and adrenalectomized (ADX) following the development of palpable tumors. Tumors which regressed after OVX and ADX were reactivated by injections of estrogen (E) and were used in explant culture. The presence of estrogen receptor (ER) was estimated by the *in vitro* uptake of ³H-E in the presence or absence of the antagonist nafoxidine hydrochloride. The addition of prolactin (P) to the excised tumor tissue in culture stimulated the ER binding capacity 3-4 fold. These results indicate that P may play an important role in the regulation of the action of E in hormone-dependent DMBA tumors. Intimate interaction between E and P at the tumor site seems to be required for tumor growth.

0672 EFFECT OF LIFETIME ADMINISTRATION OF 2-HYDROXYETHYLHYDRAZINE ON TUMORIGENESIS IN HAMSTER AND MICE. (E.) Shimizu, H. (Eppley Inst. Res. Cancer U. Nebraska Med. Ctr., Omaha) and B. Toth. *J Natl Cancer Inst* 52(3):903-906, 1974.

Solutions of 0.015% 2-hydroxyethylhydrazine (2-HEH) were administered in the drinking water to 6-week-old Syrian hamsters and 5-week-old Swiss mice; the drug treatment was continued throughout the animals' lives. In both species, the 2-HEH treatment reduced the survival time compared with nontreated controls. Among the treated hamsters, 6% of the females and 10% of the males developed hepatomas, whereas among the controls, the corresponding incidence was 0% in the females and 1% in the males. The chemical did not increase the incidence of other tumors in the hamsters, nor did it have a detectable tumorigenic effect in the mice. By standard evaluation methods, the differences in tumor incidence in the 2-HEH-treated and control groups were not statistically significant. Of the substituted hydrazines which have been tested, only 2-HEH has had no significant tumorigenic action in mice.

- 0673 BENIGN HEPATOMA AND ORAL CONTRACEPTIVES. (E.) Tountas, C. (Aretaeion Hosp., 2nd Surg. Dept., U. Athens, Greece), G. Paraskevas and H. Deligeorgi. *Lancet* 1(7870):1351-1352, 1974.

A 30-year-old woman who had been using an oral contraceptive for 3 years was admitted to the hospital with acute pain in the upper left abdomen and a palpable mass. At operation 2 days later, a large yellowish-gray nonencapsulated hemorrhagic mass was found which had almost replaced the left lobe of the liver and was covered by omentum. The tumor consisted of well-differentiated hepatic cells with vacuolated cytoplasm arranged in cords and separated by dilated sinusoids. Within the tumor, dilated large veins were seen, and no portal spaces or bile stasis were found. Surrounding the tumor, the hepatic parenchyma was normal, with mild lymphocytic infiltration at the portal spaces.

- 0674 EFFECT OF CONTINUAL DRINKING OF TILORONE SOLUTION ON METHYLCHOLANTHRENE ONCOGENESIS IN MICE. (E.) Glaz, E. T. (Dept. Pharmacol., Semmelweis Med. U., Budapest, Hungary). *Res Commun Chem Pathol Pharmacol* 8(2):405-408, 1974.

The potent interferon inducer tilorone hydrochloride was administered (50-60 mg/kg for 3 months, followed by 40-50 mg/kg thereafter) in the drinking water to inbred C57BL mice which had been injected s.c. with a single 120 µg dose of methylcholanthrene (MC). The appearance of s.c. tumors was significantly retarded in the animals treated with tilorone hydrochloride, although their life spans did not differ significantly from those of the controls treated with MC alone. Tilorone decreased both tumor and body weights significantly, but did not significantly affect the number of animals developing tumors. Several signs of chronic toxicity were observed in the tilorone-treated mice. Tilorone did not appear to have cocarcinogenic or oncogenic effects under the conditions applied. Its effect was regarded as nonspecific.

- 0675 PANCREATIC ACINAR CELL DAMAGE INDUCED BY 4-NITROQUINOLINE-1-OXIDE AND 4-HYDROXY-AMINOQUINOLINE-1-OXIDE. (E.) Konishi, Y. (Fels Res. Inst., Philadelphia, Pa.), J. A. Popp and H. Shinozuka. *J Natl Cancer Inst* 52(3):917-920, 1974.

Male Wistar and Sprague-Dawley rats were injected with 4-hydroxyaminoquinoline-1-oxide (4HAQO) (7, 13, or 20 mg/kg, i.p. or i.v.) or 4-nitroquinoline-1-oxide (4NQO) (5, 10, or 20 mg/kg, i.p.) dissolved in DMSO. A single i.p. injection of either compound induced severe pancreatic acinar-cell necrosis within 24-48 hours. The severity of the necrosis was dose dependent. With a lower dose of either agent, the lesions tended to localize in the subcapsular region of the pancreas and the periphery of the lobules. 4HAQO administered i.v. caused diffuse involvement of the pancreas, with necrosis of scattered acinar cells throughout the lobules; the two lower doses caused injury only to the acinar cells, while the highest dose caused islet-cell necrosis. The pancreatic ducts were unaffected by i.v. 4HAQO. Neither 4NQO

or 4HAQO induced any significant histologic alterations in the liver, although necrosis of the salivary gland acinar cells was consistently observed.

- 0676 MILK AS TRANSPORT AGENT FOR DIETHYLNITROSAMINE IN SYRIAN GOLDEN HAMSTERS. (E.) Spielhoff, R. (Dept. Exp. Pathol., Med. Coll., Hannover, West Germany), H. Bresch, M. Hönig and U. Mohr. *J Natl Cancer Inst* 53(1):281-282, 1974.

¹⁴C-diethylnitrosamine (¹⁴C-DEN) was injected i.p. into lactating Syrian golden hamsters. Milk and blood samples from these animals were subsequently analyzed for the injected ¹⁴C-DEN and its metabolites by thin-layer chromatography. The DEN was rapidly distributed, the maximum concentration in the blood being reached after 5 minutes. After 30 minutes, it appeared in the milk samples, maximum concentrations being reached after 45 minutes. Within 120 minutes, it disappeared from both the blood and milk. However, the total ¹⁴C activity in the milk increased 10-fold after 120 minutes, compared with the maximum concentration of DEN. The polar substances found 30 minutes after injection may have been hydroxylated metabolites, the second maximum after 240 minutes possibly having been caused by a link between these metabolites and glucuronic acid. After 8 hours, the remaining activity was possibly due to methylated lipids. Suckling infant hamsters ingested 0.0064% of the DEN injected into the mother.

- 0677 LONG-TERM TOXICITY OF SUNSET YELLOW FCF IN MICE. (E.) Gaunt, I. F. (British Industrial Biol. Res. Assoc., Carshalton, Surrey, England), P. L. Mason, P. Grasso and I. S. Kiss. *Food Cosmet Toxicol* 12(1):1-10, 1974.

Groups of 30 male and 30 female Charles River CD mice were maintained for 80 weeks on diets containing 0.2, 0.4, 0.8, or 1.6% Sunset Yellow FCF (a permitted food coloring in the United States and the EEC countries); 60 male and 60 females served as nontreated controls. The Sunset Yellow FCF treatments did not adversely affect the death rates, rates of body-weight gain, organ weights, or hematological findings. The incidence and severity of histopathological findings were similar in the treated and control mice and there was no evidence of an increased incidence of tumors in the treated animals. Thus, in mice Sunset Yellow FCF fed at levels up to 1.6% is not carcinogenic and does not exert any long-term toxic effects.

- 0678 LONG-TERM TOXICITY OF VIOLET 6B (FD & C VIOLET NO. 1) IN MICE. (E.) Grasso, P. (British Industrial Biol. Res. Assoc., Carshalton, Surrey, England), J. Hardy, I. F. Gaunt, P. L. Mason and A. G. Lloyd. *Food Cosmet Toxicol* 12(1):21-31, 1974.

Groups of 48 male and 50 female ASH-CS1 mice were maintained for 80 weeks on diets containing 0 (control), 70, 700, or 3500 ppm Violet 6B (a food coloring which is permitted in the United Kingdom but which has been banned in several other countries, including

the United States). The feces of all of the treated mice were violet colored, but the urine appeared normal, indicating that the dose was largely unabsorbed from the gastro-intestinal tract. The feeding of Violet 6B did not affect the mortality, rate of body-weight gain, or hematological picture in any of the treated groups at any time throughout the study. The incidence of histopathological findings, including tumors, was the same in the treated and control groups. Thus, the addition of Violet 6B to the diets of mice at levels up to 3500 ppm (equivalent to an intake of approximately 500 mg/kg/day) did not exert any long-term toxicological or carcinogenic effects.

- 0679 THE BINDING AFFINITY OF AFLATOXINS ON THE UTERINE OESTROGEN RECEPTOR. (E.) Kyrien, H. J. (Inst. Physiol., Univ. Munich, Germany). *Z Lebensm Unters Forsch* 5(154):285-287, 1974.

The estrogenic potency of the aflatoxins B₁, G₁, G₂ and M₁ was determined by incubating the uterine cytosol fraction of calves with tritiated 17 β -estradiol in the presence of the various aflatoxins. If the aflatoxins competed with 17 β -estradiol for binding sites on the receptor, the binding of the 17 β -estradiol was diminished. The aflatoxins B₁, G₁ and G₂ showed no affinity for the uterine estrogen receptor. Aflatoxin M₁ showed some affinity within the range from 1×10^{-7} to 1×10^{-6} molar. Compared with the endogenous estrogen, 17 β -estradiol (100%) and the stilbene derivate dienoestrol (10%) the estrogenic potency of aflatoxin M₁ is about 0.5%. The presence of the free alcoholic OH-group on C-atom 4 seems to be essential for the binding of aflatoxin M₁ to the receptor. Replacement of the OH-group by another H-atom (as in Aflatoxin B₁, G₁ and G₂) eliminated binding affinity.

- 0680 MEASUREMENTS OF LYSOSOMAL ENZYME ACTIVITY IN LIVER TUMORS INDUCED BY DIETHYLNITROSAMINE AND THE EFFECT OF CALCIPARIN (HEPARIN CALCIUM) ON THEM: A CONTRIBUTION TO THE PROBLEM OF EXPANSIVE TUMOR GROWTH. (Ger.) Platt, D. (Med. Clin. Polyclin., U. Giessen, Germany) and F. Hering. *Verh Dtsch Ges Inn Med* 78:162-163, 1972.

Hyaluronidase, β -glucuronidase, and β -acetylglucosaminidase activities were determined in the center of hepatomas, in tissue around the tumors, and in tumor-free areas of the livers of albino rats which had been given diethylnitrosamine (DENA; 5 mg/kg p.o. through an esophageal tube) over an 85-day period. Three groups of surviving rats received increasing concentrations of heparin calcium, a competitive inhibitor of hyaluronidase, for a 30-day period, while another group (controls) was treated with DENA alone for another 15 days. Enzyme activities were also determined in the livers of tumor-free rats. In tumor-free areas of the liver, hyaluronidase activities were higher in heparin-treated animals than in controls. In the tumor periphery, the activities of all enzymes except acetylglucosaminidase were higher than in controls. Hyaluronidase and β -acetylglucosaminidase activities were higher in the tumor

center than in liver preparations from tumor-free rats. Activities of all three enzymes studied were higher in the tumor periphery than in adjacent tumor-free areas of the liver. Rats treated with heparin calcium (312.5 IU/48 hr or 635 IU/72 hr) had significantly fewer hepatomas and tumors with significantly smaller diameters than the controls. These findings suggest that lysosomal enzymes in the liver break down mucopolysaccharide-protein complexes in ground substance at the edge of the tumor and enable tumor cells to invade this area.

- 0681 INHIBITION OF TUMOR PROTECTION BY A NEUTRAL FRACTION OF CIGARETTE SMOKE CONDENSATE. (E.) Akin, F. J. (Richard B. Russell Agr. Res. Ctr., Agr. Res. Serv., Dept. Agr., Athens, Ga.) and W. J. Chamberlain. *J Natl Cancer Inst* 52(2):613-615, 1974.

Cigarette smoke condensate (CSC) and two neutral sub-fractions were applied to the dorsal epidermis of female ICR Swiss mice, who were concurrently being treated with the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA) after initiation with 7,12-dimethylbenz(a)anthracene (DMBA). The tumor promoting activity of CSC was within the previously reported range, and TPA promoted tumor development in a dose dependent fashion. CSC did not alter the latent period before the first tumor appearance or the final tumor yield, but between the 8th and 12th weeks of promotion, there were more tumor bearing animals in the group receiving the highest dose of TPA than in the group receiving the same dose of TPA plus CSC. Dexamethasone prevented tumor formation in all cases but one. The ether-soluble neutral fraction (ESN) of CSC, which has marginal tumor-promoting activity, inhibited the promoting effect of TPA, as measured by delayed tumor appearance and a reduction in the number of tumor-bearing mice. The benzo(a)pyrene-containing fraction did not alter the promoting effect of TPA. Thus, anticarcinogenic substances occur naturally in tobacco.

- 0682 SMOKING, LUNG CANCER AND OCCAM'S RAZOR. (E.) Doll, R. (U. Oxford, England). *New Scientist* 61(886):463-467, 1974.

To the cancer specialist, the facts indicate that cigarette smoking is one of the principal causes of lung cancer and that the risk of developing the disease can be diminished by stopping smoking. Professor Burch argued against this conclusion, his criticism being based on five points. (1) The changes that have occurred in the national mortality rates from lung cancer cannot be wholly attributed to changes in the consumption of cigarettes. This is true. (2) He states that there has not been any real increase in the incidence of the disease at all. Features which strongly indicate that some of the increase is real include extent of the increase, its continuation into recent years, and the difference in the trends for men and women. (3) It has been hypothesized that genetic factors determine the susceptibility of the individual to the development of lung cancer and also predispose him to smoke. In the absence of adequate twin data, this hypothesis

remains unattractive. (4) In one study, a smaller number of hospital patients with lung cancer reported that they inhaled compared with the other patients in the hospital. Actually, among light smokers the disease is commoner in those who inhale than in those who do not, while the reverse may be true in heavy smokers. The significance of these data remains open to debate. (5) Between 1954-1957 and 1962-1965, the mortality from lung cancer in male doctors fell, while it continued to rise in the general population. More data is needed regarding this trend, but the difference between the trends in mortality argue against the constitutional hypothesis. There is a mass of experimental and epidemiological evidence to support the belief that cigarette smoking is one of the principal causes of lung cancer.

0683 INHIBITORY EFFECT OF 2-Br- α -ERGOCRYPTINE-METHANE-SULFONATE ON RENAL CARCINOGENESIS IN THE MALE HAMSTER. (E.) Hamilton, J. M. (Sch. Med., U. Leeds, England), A. Flaks and P. G. Saluja. *J Natl Cancer Inst* 52(6):1929-1930, 1974.

Diethylstilbestrol (DES, 0.6 mg s.c. three times/wk) was injected into two groups of male hamsters over a 9-month period and the animals were then killed. One group also received 2-Br- α -ergocryptine-methane-sulfonate (CB 154, 500 μ g s.c. five times/wk). All hamsters on DES alone developed widespread and severe renal tumors. In hamsters given CB 154 in addition, renal tumors were absent or minimal. The adeno-hypophyses of DES-treated animals showed considerable enlargement of the intermediate lobes and increased numbers of prolactin cells in the anterior lobes. Combined treatment with DES and CB 154 significantly inhibited these changes.

0684 ANGIOSARCOMA OF LIVER IN THE MANUFACTURE OF POLYVINYL CHLORIDE. (E.) Creech, J. L., Jr. (B. F. Goodrich Chem. Co., Louisville, Ky.) and M. N. Johnson. *J Occup Med* 16(3):150-151, 1974.

Between September 1971 and December 1973, three people who had been involved in the manufacture of polyvinyl chloride resins died of angiosarcomas of the liver. The first patient, aged 36 years at the time of death, had been employed for 15 years in the manufacture of polyvinyl chloride resins prior to his hospitalization for tarry stools in January 1970. Four months later, the patient was subjected to laparotomy and liver biopsy, after which he was treated with 3600 R cobalt and several intra-arterial infusions of 5 FU. During this time there was a marked distortion of the blood chemistry with severe diminution of albumin and marked increases in total bilirubin, alkaline phosphatase, LDH, and SGOT. He succumbed to the liver tumor 14 months postoperatively.

0685 A DIRECT MECHANISM OF MAMMARY CARCINOGENESIS INDUCED BY 7,12-DIMETHYLBENZ(a)ANTHRACENE. (E.) Sinha, D. (Dept. Breast Surg., Roswell Rk. Mem. Inst., Buffalo, N.Y.) and T. L. Dao. *J Natl Cancer Inst* 53(3):841-846, 1974.

Mammary adenocarcinomas in female Sprague-Dawley rats were induced by the administration of 7,12-dimethylbenz(a)anthracene (DMBA) via 2 routes: systemic administration and direct application of the carcinogen to the mammary gland. Hyperplastic alveolar nodules (HANs) were numerous in the mammary glands of all rats receiving a single injection of 5 mg DMBA, but they were never seen in the mammary glands of rats given a local application of DMBA (25-300 μ g). With this method of direct application, tumors developed only in the mammary gland where the carcinogen (300 μ g or 1 mg) was applied; induced tumors were hormone-dependent adenocarcinomas. Microscopic tumors originated in the ducts as early as 30 days after local application of the carcinogen. Thus formation of HANs was not essential in mammary carcinogenesis when DMBA was applied directly.

0686 LACK OF INDUCTION OF THYMOMAS AND OF PULMONARY ADENOMAS IN INBRED SWISS MICE BY N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Frei, J. V. (Dept. Path., Fac. Med., U. Western Ontario, London, Canada) and V. V. Joshi. *Chem Biol Interact* 8(2):131-133, 1974.

A single dose of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) (0.1-1000 mg/kg) was injected i.p. into 6-8-week-old inbred CFW/D Swiss mice. The LD₅₀ was found to be about 75 mg/kg. Thirty female mice were then treated with 60 mg/kg of MNNG. There was no significant difference in the tumor incidence in this group and a group of nontreated controls after 1 year. The results indicate that: under the conditions of this experiment, MNNG failed to induce enough O⁶-alkylguanine in the DNA of these mice; O⁶-alkylguanine is only one of several factors required for tumor induction; or O⁶-alkylguanine formation has nothing to do with tumor induction.

0687 EXPERIMENTAL BIOLOGICAL MODELS FOR TESTING THE CARCINOGENICITY OF POLYCYCLIC AROMATIC HYDROCARBONS. (Ger.) Tomingas, R. (Med. Inst. Air Hyg. Silicosis Res., U. Dusseldorf, Germany), F. Pott and W. Dehnen. *Arch Geschwulstforsch* 42(4):298-306, 1973.

In a review, primarily of their own work, the authors discuss the suitability of animal models for testing the carcinogenicity of substances in dust, industrial pollutants, or automobile exhaust. The effect which the vehicle has on the results of such tests is emphasized. Differences in the number of tumors induced by intratracheal and s.c. administration of benzo(a)pyrene (BP) in physiological saline, tri-caprylin, or polyethylene oxide are due to differences in the rates with which these vehicles are eliminated from the site of administration and whether the carcinogen is dissolved or merely suspended in them. Because tumors are induced rapidly with very small doses of carcinogen, s.c. injection of a polyethylene oxide solution is recommended as a model suitable for testing carcinogens. Similarly, inhalation studies in rats and hamsters can be speeded up by intratracheal administration of quartz dust 3

months before administration of the carcinogen or by having the animals inhale ozone for 6 hr prior to treatment with carcinogen. Such pretreatment reduces the rate at which intratracheally administered carcinogen is cleared from the lungs. Although macrophage cell cultures cannot give any information about the carcinogenicity of polycyclic aromatic hydrocarbons, they can be used to solve the problem of how these compounds are metabolized in the lung. After it was demonstrated that alveolar macrophage cultures from guinea pigs were able to take up benzo(a)pyrene and that the uptake decreased proportionally with time, this system was used to test industrial carbon black and hematite and smelting furnace dust for BP. BP concentrations can also be measured from fluorescence spectra obtained on macrophage extracts or from increases in enzyme protein since this carcinogen induces enzymes in both liver and macrophage cultures.

0688 SPECTRAL CHANGES IN LIVER MICROSOMAL CYTOCHROME P-450 FROM BENZANTHRACENE-TREATED NORMAL AND PARTIALLY HEPATECTOMIZED RATS. (E.)

Fischer, P. W. F. (Dept. Biochem., Queen's U., Kingston, Ontario, Canada) and T. Spencer. *Chem Biol Interact* 8(4):253-259, 1974.

Normal and partially hepatectomized female Wistar rats were injected i.p. with 100 mg/kg benzantracene (BA). The cytochrome P-450 component of the mixed function oxidase in the liver microsomes was modified to a species with a reduced CO complex spectral peak at 448 nm in the BA pretreated animals. In addition, the P-450 content of the microsomes was increased in the BA-treated rats, the effect being greater in the partially hepatectomized animals. When protein synthesis was blocked by the administration of actinomycin D or puromycin, there was a decrease in the P-450 content of the microsomes, although BA was still able to cause the conversion to the modified form in young animals. The change also occurred *in vitro* when microsomes from young female rats were treated with BA; this change did not occur in cytochrome P-450 from adult females. The ability of BA to catalyze the change in the cytochrome structure appears to depend on the animal's estrogen level.

0689 KARYOMETRIC AND CYTOPHOTOMETRIC STUDIES OF LIVER REGENERATION AFTER PARTIAL HEPATECTOMY IN CHRONIC THIOACETAMIDE INTOXICATION. (Ger.)

Bader, G. (Sudstadt Reg. Hosp., Rostock, Germany), N. G. Bader and K. J. Stiller. *Exp Pathol (Jena)* 9(1/2):9-15, 1974.

Young male Wistar rats were partially hepatectomized after administration of 25 mg/kg/day thioacetamide (TA) p.o. in drinking water for 3-4 months or 6-9 months. Liver biopsies were removed 24 hr after hepatectomy, and rats were sacrificed after 48 hr and autopsied. After staining of fixed, paraffin-embedded liver sections with gallocyanin-chrome alum, the diameters of 500-1000 round nuclei, including their nucleoli, were measured and the nuclear DNA content was determined cytophotometrically, using Feulgen's

stain. Treatment of rats with TA delayed liver regeneration after hepatectomy. Examination of small hepatic pseudolobules showed that the diameters of nucleoli were increased 24 and 48 hr after hepatectomy. Increases in the rate of RNA metabolism induced by hepatectomy were greater in rats treated with TA for 3-4 months than in those treated for 6-9 months; these increases were more evident 24 hr after hepatectomy than after 48 hr. This effect was observed in cells with diameters in the tetraploid range, suggesting that the increase in RNA metabolism induced by hepatectomy occurs independently of TA-induced inhibition of RNA metabolism. After hepatectomy only slight increases occurred in DNA synthesis. The presence of large numbers of diploid cells in both groups of TA-treated rats is considered a manifestation of precancerous proliferation of liver tissue. The increase in the number of diploid cells resulting from regeneration was associated with an increase in the mitotic index, suggesting that cell proliferation may occur by indirect division of the nucleus. Loss of residual glycogen and increasing dispersion of the ergastoplasm were still observed 48 hr after hepatectomy in TA-treated rats.

0690 THE FORMATION OF METHYLATED BASES IN DNA BY DIMETHYLNITROSAMINE AND ITS RELATION

TO DIFFERENCES IN THE FORMATION OF TUMOURS IN THE LIVERS OF GR AND C3Hf MICE. (E.) den Engelse, L. (Netherlands Cancer Inst., Amsterdam). *Chem Biol Interact* 8(5):329-338, 1974.

The metabolism of dimethylnitrosamine (DMNA) was measured in the livers of GR male and C3Hf male and female mice; the methylation of DNA by DMNA was also studied. Continuous DMNA administration results in the development of vascular liver tumors in C3Hf female mice, whereas male C3Hf animals show a high incidence of hepatomas. GR males show a low susceptibility to the formation of liver tumors after DMNA treatment. The N-demethylation of DMNA by liver microsomes occurred at similar rates in all of the C3Hf animals, but was greatly increased in the GR males. Five and 48 hours after a single injection of (¹⁴C)DMNA, the amounts of O⁶-methylguanine (O⁶-MeGua), 7-methylguanine (7-MeGua), 1-methyladenine (1-MeAde), and 3-methyladenine (3-MeAde) were similar for male and female C3Hf mice, with the possible exception of 7-MeGua which seemed to be somewhat elevated in the females. O⁶-MeGua disappeared from C3Hf liver DNA with an apparent half-life of about 24 hours. Especially 48 hours after injection, the GR liver DNA was methylated to a greater extent than was the C3Hf liver DNA. This result antiparallels the incidence of tumors after DMNA in the two strains and may be explained in terms of the differences in the rate of the N-demethylation of DMNA. The higher methylation of GR liver DNA appears to be caused by a higher production of CH₃⁺ ions in the GR liver. This conclusion is supported by the fact that DMNA metabolism in the liver was greatly increased after fasting. The data indicate that neither the metabolism of DMNA or DNA methylation by this carcinogen in the livers of the experimental mice correlates

with the formation of hepatomas after DMNA administration.

0691 VARIATIONS IN THE ANTIGENICITY AND THE GROWTH RATE FOR MURINE SARCOMAS INDUCED BY A CHEMICAL CARCINOGEN. (It.) Pierotti, M. (Natl. Inst. Tumor Res. Ther., Milan, Italy) and S. Menard. *Tumori* 60(1):33-44, 1974.

The relationship between antigenicity, tumor growth rate, and tumor latent period for 7,12-dimethylbenz(a)anthracene (DMBA)-induced sarcomas was studied in three groups of mice. Antigenicity is defined as the difference in the mean number of days between s.c. inoculation of a tumor cell suspension and the appearance of tumors measuring 15 mm between normal adult and immunosuppressed mice. Immunosuppression consisted of thymectomy followed, after 24 hr, by whole-body irradiation with 450 r. A study of 36 sarcomas (30 fibrosarcomas and 6 rhabdomyosarcomas) which developed after inoculation into BALB/c mice showed that tumors with a short latent period (less than 20 wk) were significantly more antigenic than those with a longer latent period. There was also an inverse relationship between the antigenicity and growth rate. Of the three tumors which were exceptions to this rule, two were rhabdomyosarcomas which appeared after 12 wk. Serial transplantations of a DMBA-induced fibrosarcoma were performed in normal and immunosuppressed C3Hf mice showed an inverse relationship between the growth rate and antigenicity during serial passages. In another experiment in C3Hf mice serial passages of two antigenic tumors with different antigens showed that antigenicity decreased and the growth rate increased during serial passage of both tumors. This discounts the hypothesis that immunological selection occurs or that the growth of cell clones with a low antigenicity and high growth rate is favored. It is more likely that during tumor proliferation the transformed cells gradually lose mechanisms controlling the growth rate simultaneously with a decrease in membrane antigenicity.

0692 DEVELOPMENT OF MALIGNANT NEURINOMAS IN THE OFFSPRING OF SPRAGUE-DAWLEY RATS AFTER LOCAL APPLICATION OF ETHYLNITROSOUREA TO THE SKIN DURING PREGNANCY. (Ger.) Graw, J. (German Cancer Res. Ctr., Heidelberg), W. J. Zeller and S. Ivankovic. *Z Krebsforsch* 81(2):169-172, 1974.

Circular plaster bands extending from the neck to the sacral region were placed around eight pregnant Sprague-Dawley rats. Each band had a window, measuring 2 x 2 cm, through which ethylnitrosourea (50 mg/kg in a 10% acetone solution) was applied to the shaved skin of six rats on days 16-22 of gestation. The bands prevented rats from licking carcinogen off their skin. The skin was scarified in three of the six treated animals; two untreated pregnant rats served as controls. Of the 35 offspring in the treated group, 21 were reared. Between age 39-202 days, five of the offspring died of pneumonia. Of the remaining 16 offspring, nine developed malignant tumors. The first tumor appeared at age 221

days. Eight malignant tumors of the nervous system consisted of two malignant neurinomas of the cauda equina and root of the mesentery, resp.; four mixed gliomas of the brain; and two cerebral ependymomas. Another offspring developed a solid mammary adenocarcinoma which metastasized to the lungs. Skin scarification had no effect on tumor location or induction time, and the frequency of tumors was about the same in both treated groups. No malignant tumors were observed in the 122 offspring of controls during an observation period of 700 days.

0693 CARCINOGENIC PROPERTIES OF HYDRAZOBENZENE. (Rus.) Pliss, G. B. (N.N. Petrov Inst. Oncol., Leningrad, USSR). *Vopr Onkol* 20(4):53-57, 1974.

Carcinogenic properties of hydrazobenzene were studied in chronic experiments in 163 rats and 110 2-month-old CC57 mice. A suspension of the drug in sunflower seed oil was injected s.c. over a period of about 588 days (40 mg/wk per rat and 5 mg/wk per mouse), added to fodder (30 mg 5 times/wk), or applied to the skin (30 mg 5 times/wk in rats and 2 mg 3 times/wk in mice). Rats received a total of 3.8 g by injection or 12.57 g p.o., while mice received a total of 370 mg by injection or 360 mg on skin. Primary tumors were first detected on the 179th-188th day. The minimal latent period was 188 days after s.c. injection and 372 days after p.o. administration. Neoplasms occurred after s.c. injection in 36.6% of mice and 22.6% of rats; after skin application, in 22.2% of mice; and after p.o. administration, in 50% of mice and 50% of rats. Tumors of the uterus, mammary and Zimbal glands, liver and spleen, and lymphoid leukemia were observed in rats. Subcutaneous rhabdomyosarcoma, pulmonary adenoma, leukemia, liver tumors, and skin cancer were observed in mice. Frequency varied with route of administration. Thus, hydrazobenzene induces tumors similar to those observed after exposure to benzidine and its derivatives. Partial conversion of hydrazobenzene may occur in the acid environment of the stomach, leading to a tumorigenic effect. Rearrangement of hydrazobenzene into benzidine and diphenylene in acid medium has been demonstrated by paper chromatography. Since intoxication and cirrhotic liver changes were absent in these experiments, the entire carcinogenic effect of hydrazobenzene cannot be attributed to its conversion to benzidine.

0694 EFFECT OF DIMETHYLSULFOXIDE AS A CARCINOGEN IN INDUCED CARCINOGENESIS OF THE SKIN IN MICE. (Rus.) Finogenova, M. A. (Inst. Nutrition, Acad. Med. Sci., USSR). *Biull Eksp Biol Med* 77(2):75-76, 1974.

The effect of dimethylsulfoxide (DMSO) as a solvent for 3-methylcholanthrene (MC) was studied on skin of the interscapular region in male CBA x C57BL hybrid mice. 0.02 ml of MC in 0.25 and 0.5% benzene or DMSO solution was applied once per week until the end of the experiment. Group 1 received 0.25% MC solution in DMSO, while group 2 (control) received

a 0.25% MC in benzene. Group 3 received 0.5% MC solution in DMSO while group 4 (control) received 0.5% MC in benzene. In group 1, the first papilloma was observed 3 weeks, and the first carcinoma 1 week earlier than in group 2. The mean latent period was 0.8 wk shorter for papillomas and 0.4 wk shorter for carcinomas; this is statistically significant. In group 3, in which the concentration of MC was doubled, the first papilloma and the first carcinoma were observed one wk earlier, and the mean latent period for each was 1 week shorter. Significant differences in the mean number of papillomas per mouse in control and experimental groups were noted. The accelerating effect of DMSO on skin carcinogenesis may be explained by an increase in the effective dose of the carcinogen as a result of its more rapid penetration, through the keratin layer of the skin. Moreover, DMSO increases the thymidine labeling index in tissue culture, and it is known that tissue with increased DNA synthesis is more sensitive to the effect of the carcinogen.

0695 EFFECT OF VARIOUS CARCINOGENIC AND NON-CARCINOGENIC SUBSTANCES ON DEVELOPMENT OF BLADDER TUMORS IN RATS INDUCED BY N-BUTYL-N-(4-HYDROXYBUTYL)NITROSOAMINE. (E.) Ito, N. (Cancer Ctr. Inst., Nara Med. U., Japan), K. Matayoshi, K. Matsumura, A. Denda, T. Kani, M. Arai and S. Makiura. *Gann* 65(2):123-130, 1974.

The effects of various carcinogenic and noncarcinogenic substances on the development of N-butyl-N-(4-hydroxybutyl)nitrosoamine-induced urinary bladder tumors were studied histologically using male Wistar rats. Pre- or post-treatment with N-nitrosopiperidine, N-nitrosomorpholine, diethylnitrosoamine, or N-2-fluorenylacacetamide inhibited the incidence of urinary bladder tumors induced by 0.05%/day (in drinking water for 8 weeks) N-butyl-N-(4-hydroxybutyl)nitrosoamine. The production of hyperplasias and papillomas in the urinary bladder epithelium was not inhibited by pre- or post-treatment with several carcinogens, including 4-chloroacetanilide. After pretreatment with various hepatotoxic and nephrotoxic substances, 4-chloroacetanilide and 1-naphthyl isothiocyanate inhibited the production of urinary bladder cancer induced by N-butyl-N-(4-hydroxybutyl)nitrosoamine, the latter especially inhibiting not only the development of cancer but also the development of hyperplasia and papilloma of the urinary bladder epithelium. When the two carcinogens, N-butyl-N-(4-hydroxybutyl)nitrosoamine and N-2-fluorenylacacetamide, were administered together, they acted synergistically in inducing urinary bladder cancer. DL-tryptophan promoted their action in producing urinary bladder tumors.

0696 RELATION OF STILBESTROL EXPOSURE *IN UTERO* TO VAGINAL LESIONS IN ADOLESCENCE. (E.) Carrington, E. R. (Med. Coll. Pennsylvania, Philadelphia). *J Pediatr* 85(2):295-296, 1974.

The incidence of clear-cell adenocarcinoma in women exposed *in utero* to diethylstilbestrol is not accurately known but is apparently very low. However, the oc-

currence of benign lesions in these exposed young females ranged from 30 to 40%. Of the benign lesions, the most common is adenosis, usually arising in the submucosal area and sometimes replacing the surface epithelium. Other benign features include the occurrence of transverse ridges in the upper vagina or over the ectocervix in which areas of adenosis may be found. A florid or strawberry red appearance of involved areas is characterized. The finding of adenosis in tissues adjacent to adenocarcinoma has raised the question as to whether adenosis represents a premalignant lesion. Most common symptoms include vaginal bleeding or discharge, and, less frequently, pain. Many patients remain asymptomatic. Clinical evaluation of exposed females is encouraged and should include inspection of cervix and vagina, collection of vaginal and cervical smears for cytologic exam and palpation to determine the presence of nonvisible submucosal lesions. Colposcopic examination, Schiller's stain, and biopsy of abnormal areas should be performed. The drug, diethylstilbestrol, was widely used during the 1950s and 1960s and thus it will be necessary to carry out such examinations for some time to come.

0697 CARCINOGENICITY OF BRACKEN AND SHIKIMIC ACID. (E.) Evans, I. A. (Dept. Biochem., U. Coll. North Wales, Bangor) and M. A. Osman. *Nature* 250(5464):348-349, 1974.

TF1 strain mice were given single i.p. injections of aqueous shikimic acid. Of 14 animals, 9 had cancerous and precancerous lesions. Of 57 control mice treated the same way, none developed any neoplasms at all, indicating that, for this strain of mice, the spontaneous tumors of old age are not encountered before age 15 months. The leukemias which developed in the mice injected with shikimic acid displayed the variety of classic features including widespread dispersal through the peritoneal and pleural cavities and involvement of organs such as lymph nodes, spleen, liver, and kidney. The reticulum cell A leukemia was extremely disseminated. A mouse test for the production of dominant lethal mutations was conducted using mature male mice of the TF1 strain. One group was injected with shikimic acid (25 mg in 0.5 ml water, i.p.) and a second group had an oral dose of 80 mg in 0.2 ml water by stomach tube. These animals were mated with virgin females and the females examined and scored for total implantations, early deaths and late deaths. The Mutagenic Index was thus determined. Taken over the whole 8 week period, the average control figure was 4.4%, the oral shikimic group reached 13.6% and these injected i.p. reached a maximum of 22.1%.

0698 ACTION OF TRANSCRIPTION AND TRANSLATION INHIBITORS ON THE ENHANCEMENT OF DRUG HYDROXYLATION AND GLUCURONIDATION BY 3-METHYLCHOL-ANTHRENE AND PHENOBARBITAL. (E.) Vainio, H. (Dept. Physiol., U. Turku, Finland), A. Aitio and O. Hänninen. *Int J Biochem* 5(2):193-200, 1974.

A single dose of both phenobarbital and 3-methyl-

cholanthrene induced microsomal mixed function oxidase complex and UDP glucuronyltransferase (*p*-nitrophenol) in 24 hr in Wistar rat liver. However, the increases differed in amplitude. Both the aryl hydrocarbon hydroxylase and *p*-nitroanisole O-demethylase activities were enhanced by 3-methylcholanthrene. Phenobarbital increased the O-demethylation of *p*-nitroanisole without affecting aryl hydrocarbon hydroxylase activity. Actinomycin D (0.4 mg/kg) did not block the rise in mixed function oxidase activity, but significantly inhibited induction of UDP glucuronyltransferase caused by phenobarbital or 3-methylcholanthrene administration. The higher dose, 0.8 mg/kg, blocked the induction of both mixed function oxidase complex and UDP glucuronyltransferase totally. Cycloheximide (1 mg/kg) partially inhibited the increase of both drug oxidation and glucuronidation in that the induction caused by phenobarbital was almost totally blocked, but that achieved by 3-methylcholanthrene was only slightly inhibited. These data demonstrate that the microsomal mixed function oxidase complex behaves rather differently toward the inhibitors of protein synthesis after induction with phenobarbital or 3-methylcholanthrene. The two types of microsomal mixed function oxidase and UDP glucuronyltransferase are probably under separate control mechanisms as far as the biosynthesis is concerned. The difference in the sensitivity towards low doses of actinomycin D can, however, also be due to the differences in the life-span of the specific RNAs.

0699 ASPECTS OF EXPERIMENTAL HEPATOCARCINOGENESIS. PART I. EARLY HYPERPLASTIC FOCI.

(E.) Timme, A. H. (Groote Schuur Hosp., Capetown, South Africa). *S Afr Med J* 48(16):698-701, 1974.

A basic maize diet containing 0.05% w/w of *p*-dimethylaminoazobenzene was fed to 100 male rats for periods up to 20 weeks. Light and electron microscope features of early hyperplastic lesions were studied. Light microscopy showed that the livers were obviously cirrhotic and many carcinomas had developed. After a prolonged search, 3 foci were located which were composed of islands of lightly basophilic cells containing only traces of cytoplasmic glycogen. The cells were slightly larger than those surrounding them. Occasional mitotic figures were observed. Electron microscopy revealed nuclei enlarged with a round or slightly ovoid shape. Nucleoli were moderately hypertrophied. The rough endoplasmic reticulum was composed of cisternae, usually closely applied to the mitochondria. The smooth endoplasmic reticulum was poorly developed. The cytoplasmic matrix contained numerous polysomal aggregates, whereas glycogen was sparse. In some cells the intramitochondrial granules were greatly reduced in number or absent altogether. Liver parenchyma surrounding the nodules usually showed a noticeable increase in the smooth endoplasmic reticulum while the rough endoplasmic reticulum was extensively disorganized and often visibly degranulated. The over-all ultrastructural characteristics of the liver cells comprising these foci are distinct from liver cells undergoing physiological division. Some features suggest embryonic hepatocytes and even tumor cells. It is suggested that

they are not reparative in character, but represent a specific response to the ingestion of the carcinogen and are probable starting points in the formation of large hyperplastic nodules.

0700 SERIAL ENDOSCOPIC EVALUATION OF EXPERIMENTAL GASTRIC CANCER. (E.) Suawa, C.,

(Wayne State U. Sch. Med., Detroit, Mich.), C. E. Lucas and A. J. Walt. *Gastrointest Endosc* 20(3): 105-107, 1974.

Attempts to produce experimental gastric cancer were made in 18 dogs by adding N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) to the drinking water (80 mg/l). Chronic ulcers were made in the body and antrum of the stomach of these dogs by intramural injection of dilute acetic acid 1 month after starting the carcinogen. Endoscopy and biopsy were performed monthly up to 15 months to allow visual and histological evaluation. At 3 months almost all dogs developed superficial depressed white-based antral erosions with occasional bleeding. The mucosa overlying the incisura angularis appeared irregular and depressed with development of converging folds having abrupt alterations, suggesting, in the converging folds, an endoscopic diagnosis of superficial early cancer. At 9 months, 7 of 8 dogs had well defined ulcers which appeared malignant endoscopically and were confirmed by histology to be either malignant or to show atypical epithelium. Diffuse spread to the proximal stomach was present in 1 dog at 1 year. MNNG slowed the rate of acetic acid ulcer healing in both the antrum and body of the stomach but did not cause malignant transformation nor prevent complete healing of the ulcers. These results indicate the usefulness of endoscopy in studying experimental gastric cancer.

0701 EFFECT OF THE BLADDER CARCINOGEN N-[4-(5-NITRO-2-FURYL)-2-THIAZOLYL] FORMAMIDE ON NUCLEIC ACIDS AND TOTAL PROTEIN CONTENT OF BLADDER EPITHELIUM UNDERGOING MALIGNANT CHANGE. (E.)

Pai, S. H. (Methodist Hosp. Brooklyn, N.Y.), L. Amaral, S. Werthamer and F. G. Zak. *Invest Urol* 11(5):392-395, 1974.

The effect of an 11 week diet of N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide on the biochemistry of the urinary bladder epithelial cell of the male Sprague-Dawley rat was investigated. The carcinogen altered the synthesis of DNA, RNA, and protein within 1 week's time as well as altered the amounts of the DNA, RNA, and protein in the nucleus and cytoplasm, and the volumes of both the nucleus and cytoplasm of epithelial cells of the urinary bladder of the rat. The feeding of this carcinogen appears to affect the synthesis of DNA in a nonconsistent manner since, at different intervals during the experiment, there appeared inhibitions and activations of such synthesis. Microspectrophotometric determinations of nuclear DNA classes of these cells suggest that there is a gradual increase in the percentage of the cells containing nuclei of higher ploidy than the corresponding controls. It is sug-

gested that there must have been bursts of DNA synthesis occurring at intervals which were not examined. During these 11 weeks, both synthesis and total amounts of cytoplasmic RNA and protein are generally lower than controls. Thus the feeding of this carcinogen to rats altered certain biochemical parameters of urinary bladder epithelial cells. The use of the tools and technique of this study may prove helpful, in the absence of histologic criteria, to identify epithelial cells of the urinary bladder undergoing transformation.

0702 THE SIGNIFICANCE OF BIOGENIC AMINE CONTENTS IN ACTIVE CELLS OF CONNECTIVE TISSUE DURING TUMOR GROWTH. (Ukr.) Mel'nychenko, H. V. (Inst. Problems Oncol., Kiev, USSR) and L. I. Bobro. *Dopovidni Akad Nauk Ukrain RSR* [B] (10):933-936, 1973.

Changes in the histamine and serotonin contents and the monoaminoxidase (MAO) activity were studied in 80 female rats given dimethylbenzanthracene (DMBA) i.v. (dose unspecified), either alone or in combination with anticollagen serum (ACS) during the initial period of tumor development. Examinations were made of connective tissue surrounding proliferating epithelial cells during the precancerous period and of cancer nodes in the mammary glands. A simultaneous study was made of the enterochromaffin apparatus in the duodenum since this is the major site where serotonin is produced in the body. During carcinogenesis progressive decreases occurred in the serotonin content of the enterochromaffin apparatus in the intestine and in connective tissue surrounding proliferating epithelial cells or tumor nodes. The histamine content and MAO activity increased in reactive connective tissue. When ACS was administered with DMBA, the percentage of tumors obtained decreased and their latent period increased. Increases occurred in the serotonin content of the enterochromaffin apparatus and reactive connective tissue, while decreases occurred in the histamine content and MAO activity in these areas. It appears that serotonin competes with histamine in the connective tissue system. Accumulation of histamine in connective tissue cells during carcinogenesis appears to be a sign of tissue damage.

0703 CARCINOGEN STANDARD. A LETTER TO THE ASSISTANT SECRETARY, OCCUPATIONAL SAFETY AND HEALTH - AND A RESPONSE. (E.) Stockinger, H. E. (Committee Threshold Limits, ACGIH, Cincinnati, Oh.). *J Occup Med* 16(2):119-120, 1974.

The carcinogens appearing in the "Emergency Temporary Standard of Certain Carcinogens" would be more appropriately listed by dividing them into substances which are known human carcinogens and those which have been found to be carcinogenic in experimental animals only. For example, 3,3'-dichlorobenzidine, dimethyl sulfate, ethylenimine, and beryllium have not been found to be carcinogenic for industrial workers, although they are carcinogenic for experimental animals under certain laboratory conditions. 4,4'-Methylene-bis-(2-chloroaniline) is carcinogenic for rats, but has not been shown to be

carcinogenic for dogs. Those substances in industrial use which have proven carcinogenic in man can be divided into those for which a threshold limit value (TLV) has been assigned (e.g., asbestos, nickel carbonyl) and those for which no TLV has been assigned (e.g., benzidine and its salts and 4-nitrodiphenyl). For the latter substances, no exposure or contact by any routes should be permitted. Regarding substances have induced cancer in animals under appropriate experimental conditions (e.g., 2-acetylaminofluorene, beryllium, and ethylenimine), worker exposure by all routes should be reduced to a minimum.

0704 STUDIES ON THE EFFECT OF DIFFERENT VIRUSES ON BENZO(a)PYRENE CARCINOGENESIS. (Ger.) Pfeiffer, E. H. (Hyg. Inst., U. Mainz, Germany) and Z. Graf. *Zentralbl Bakteriol Hyg [Orig B]* 159(1): 1-9, 1974.

The number of mice developing tumors and the latent periods for these tumors were studied in female NMRI mice which had been injected with benzo(a)pyrene (BP 10, 50, or 100 µg dissolved in tricaprilyn s.c.) and, 12 days later, with vaccinia, poliomyelitis type 2, or ECHO type 11 virus. The mice were about 4-wk old at the beginning of the experiment. A significant increase in the number of animals developing tumors was observed among mice given 10 µg BP followed by vaccinia virus inoculation (55 tumors vs. 44 in the control group after 88 wk). Poliomyelitis and ECHO viruses did not enhance tumorigenesis in this group. Among the mice given 50 µg BP, vaccinia virus significantly decreased the number of tumors produced (65 vs. 79 in controls). Neither ECHO nor poliomyelitis virus had any effect with this dose of BP. When mice were given 100 µg BP, infection with all three viruses significantly reduced the number of mice which developed tumors. Except for the group of mice given 50 µg BP and infected with poliomyelitis virus, where the latent period was 5 wk longer than in controls, virus infection had no appreciable effect on the latent period of tumors induced with BP. Despite this one significant result, it is concluded that viral infection has no effect on the latent period of these tumors.

0705 ISOLATION AND PROPERTIES OF THE PRINCIPAL LIVER PROTEIN CONJUGATE OF A HEPATIC CARCINOGEN. (E.) Sorof, S. (Inst. Cancer Res., Philadelphia, Pa.), B. P. Sani, V. M. Kish and H. P. Meloche. *Biochemistry* 13(12):2612-2620, 1974.

Certain cellular proteins of unknown function are preferred targets of chemical carcinogens during cell transformation *in vivo* and *in vitro*. Adult CFN livers were maintained on synthetic diets containing 0.058% of the hepatic azocarcinogen, 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB). After 15-18 days, the livers were removed and the principal liver azoprotein (h2-5S) was isolated and purified. The h2-5S azoprotein was reproducibly isolated from 50-mg samples of the livers of the treated rats. The azoprotein was 88-91% pure as shown by disc

gel electrophoresis in SDS gels. The molecular weight of the azoprotein subunit was shown by polyacrylamide gel electrophoresis in sodium dodecyl sulfate and by amino acid analysis to be 44,000. The azoprotein consists of two indistinguishable subunits which are not disulfide linked in a molecule of 88,000 molecular weight. The azoprotein molecule contains an average of two bound azocarcinogen residues per two subunits. The limiting amino acids in the protein are tyrosine, tryptophan, and methionine, which are present to the extent of two, two, and five residues per subunit, respectively. This characterization of the principal azoprotein of rat liver provides the basis for its ultimate identification and for the subsequent determination of its possible importance in liver carcinogenesis by aminoazo dyes.

- 0706 ASSOCIATIONS BETWEEN TUMOR TYPES IN A LARGE-SCALE CARCINOGENESIS STUDY OF CF-1 MICE. (E.) Breslow, N. E. (Int. Agency Res. Cancer, Lyon, France), N. E. Day, L. Tomatis, and V. S. Turusov. *J Natl Cancer Inst* 52(1):233-239, 1974.

Crude associations between tumor types found at necropsy in a multigenerational carcinogenesis experiment involving over 4000 CF-1 mice were demonstrated, in certain cases, to arise spuriously from the grouping of animals by treatment (DDT in the diet or urethan in drinking water) and/or from similarities in the age-specific tumor prevalence curves. When adjusted for these two factors, statistically significant associations nevertheless remained: Lymphomas were negatively related to hepatomas, lung adenomas, and mammary and ovarian tumors, and positively associated with bone tumors. With the possible exception of the relationship between hepatomas and lymphomas, negative associations are thought to be an artifact due to a competing-risks phenomenon. The lone positive relationship could reflect a common viral etiology.

- 0707 NITROSATION OF d-N,N'-BIS(1-HYDROXYMETHYL-PROPYL)ETHYLENEDIAMINE, AN ANTITUBERCULAR DRUG. (E.) Montesano, R. (Int. Agency Res. Cancer (IARC), Lyon, France), H. Bartsch and H. Bresil. *J Natl Cancer Inst* 52(3):907-910, 1974.

The product of the nitrosation of the antitubercular drug Ethambutol (d-N,N'-bis(1-hydroxymethylpropyl)ethylenediamine) with NaNO_2 was characterized as a dinitroso derivative by elemental, NMR, infrared, UV, and mass spectrometric analyses, as well as by conversion into a 0,0-diacetyl derivative. The nitrosation reaction gave a maximal yield at pH 3 after 60 minutes. The new product was identified as d-N,N'-bisnitroso-N,N'-bis(1-hydroxymethylpropyl)ethylenediamine (II). It was converted into d-N,N'-bisnitroso-N,N'-bis(1-acetoxymethylpropyl)ethylenediamine. The toxic effects of II were examined in BALB/c mice. All animals given 70-80 mg/kg II orally died within 12 hours of liver necrosis. Ethambutol in combination with other drugs is ad-

ministered for long periods of time in substantial doses to humans, and the nitrosation with nitrate could occur in the human stomach.

- 0708 MODIFIED SYSTEM *IN VITRO* FOR THE METABOLISM OF 2-ACETYLAMINOFLUORENE. (E.) Baetcke, K. P. (Natl. Ctr. Toxicol. Res., Food Drug Admin., Jefferson, Ark.), B. J. Gough and T. E. Shellenberger. *Biochem Pharmacol* 23(12):1745-1752, 1974.

A modified *in vitro* system for the metabolism of 2-acetylaminofluorene (2-AAF) depends upon the utilization of an NADPH-generating system, small amounts of microsomal protein and substrate, and the utilization of N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES) buffer. With these modifications, the metabolism of 2-AAF *in vitro* is linear with time and after 30 minutes, the formation of N-hydroxy-2-acetylaminofluorene (N-OH-2-AAF) represented 30% or more of the original 2-AAF. Differences in the metabolism of 2-AAF in male BALB/c mice fed different diets were determined. The liver microsomes of mice maintained on Purina chow metabolized 30% more of the added 2-AAF to N-OH-2-AAF *in vitro* than did mice receiving a synthetic diet.

- 0709 ASBESTOSIS AND CARCINOMA OF THE LARYNX: A POSSIBLE ASSOCIATION. (E.) Libshitz, H. I. (Dept. Radiol., Thomas Jefferson U. Hosp., Philadelphia, Pa.), M. S. Wersbba, G. W. Atkinson and M. E. Southard. *JAMA* 228(12):1571-1572, 1974.

Within the past 3 years, three patients were admitted to a Philadelphia hospital with primary laryngeal cancer, a history of exposure to asbestos, and intrathoracic changes on their chest roentgenograms consistent with asbestosis. The patients were all males between the ages of 54 and 65 years at first admission, and all had a history of heavy cigarette smoking. Although it is difficult to ascertain the precise causative role, if any, of asbestosis as a factor in the development of laryngeal carcinoma in these patients, the possibility of an association between these two diseases is suspected. It is also possible that cigarette smoking and asbestos exposure act synergistically in the development of one or both diseases.

- 0710 PINOCYTOSIS BY HUMAN ALVEOLAR MACROPHAGES: COMPARISON OF SMOKERS AND NONSMOKERS. (E.) Yeager, H., Jr. (Georgetown U. Sch. Med., Washington, D.C.), S. M. Zimmet and S. L. Schwartz. *J Clin Invest* 54(2):247-251, 1974.

Alveolar macrophages were collected from cigarette smokers and nonsmokers by bronchial lavage through a fiberoptic bronchoscope. The cells were incubated in a chemically defined medium containing (^{14}C) sucrose (0.36 mM) and varying concentrations (1-30%) of rabbit serum. Pinocytosis was assessed by the cellular uptake of isotope over periods of 30, 75, and 120 minutes. The pinocytic activity of the cells from the smokers was dependent on the serum concentration, increasing uptake being

associated with increasing amounts of serum. At each concentration, the uptake of radioactivity by the nonsmokers' cells was greater than that of the smokers' cells; the uptake by the nonsmokers' cells was independent of the serum concentration. The uptake of (^{14}C) sucrose by the macrophages was energy dependent. The DNA/protein ratios in the two groups of cells were not significantly different. The decreased level of pinocytic activity in the smokers' alveolar macrophages may represent a form of reticuloendothelial blockade.

0711 CARCINOGENICITY IN MICE OF SOME FATTY ACID METHYL ESTER. 1. SKIN APPLICATION. (E.)

Arffmann, E. (Dept. Path., Aalborg Hosp., Copenhagen, Denmark) and J. Glavind. *Acta Pathol Microbiol Scand (A)* 82(1):127-136, 1974.

Two highly carcinogenic oxygen-containing derivatives of unsaturated fatty acids, methyl 12-oxo-*trans*-10 octadecenoate and methyl hydroxyoctadecadienoate, were applied to the interscapular skin of male and female ST/a mice, and their carcinogenic and promoting activities compared to those of methyl oleate, croton oil, and/or 7,12-dimethylbenz(a)anthracene. Both the unsaturated fatty acid derivatives were potent promoters of skin papilloma induction. The genesis of malignant skin tumors was promoted by methyl oleate and oxooctadecenoate, and all three methyl esters were only weakly active as complete skin carcinogens. Systematically, all of the esters promoted the induction of malignant lymphomas, methyl oxooctadecenoate being the most active. Even without preceding initiation, this ester and methyl oleate showed some activity in lymphoma carcinogenesis. Thus, methyl oxooctadecenoate is the most active ester in the induction of tumors, its effect being essentially one of a promoter. In general, the female mice were more susceptible to the induction of skin tumors and lymphomas than the males.

0712 PERSISTENT CHANGES INDUCED BY SUBCARCINOGENIC DOSES OF 3'-METHYL-4-(DIMETHYLAMINO)

AZOBENZENE IN RAT LIVER. (E.) Ogawa, K. (Sapporo Med. Coll., Japan), A. Kaneko, T. Minase and T. Onoe. *Gann* 65(2):109-117, 1974.

The persistence of the histological and enzymic alterations induced by subcarcinogenic doses of 3'-methyl-4-(dimethylamino)-azobenzene (3'-Me-DAB) was studied using the livers of male Wistar rats. When the animals were fed by a diet containing 0.06% 3'-Me-DAB for 2 weeks, marked degeneration of the hepatocytes was observed, and when this diet was continued for 4-6 weeks, a larger number of the original hepatocytes were replaced by hepatocytes which seemed to have been transformed from proliferating cholangiolar cells. In conjunction with these changes, the activities of glucose-6-phosphatase (G-6-Pase) and acid phosphatase decreased markedly, while the activity of cathepsin increased and the isozyme pattern of aldolase was altered. Twenty-four weeks after cessation of the 6-week feeding program, the biochemical para-

meters returned to near normal, while slight histological changes remained evident. The treated livers showed a focus consisting of altered liver cells which usually showed decreased G-6-Pase activity with occasionally decreased adenosine triphosphatase (ATPase) activity. The altered cells contained a large amount of cytoplasmic glycogen which did not disappear even after 12 hours of fasting. When the rats were partially hepatectomized mitotic abnormalities were frequently observed. The persistent alterations were more prominent in rats fed the dye for 4-6 weeks than in those treated for only 2 weeks.

0713 POTENTIAL CARCINOGENS. I. CARCINOGENICITY OF SOME PLANT EXTRACTS AND THEIR TANNIN-CONTAINING FRACTIONS IN RATS. (E.) Pradhan,

S. N. (Coll. Pharm. Pharmacol Sci., Howard U., Washington, D.C.), E. B. Chung, B. D. Paul and G. J. Kapadia. *J Natl Cancer Inst* 52(5):1579-1582, 1974.

NIH Black rats were given ≤ 75 s.c. injections weekly of the total aqueous extracts of *Krameria ixina* (plant sans root), *K. triandra* (root), *Acacia villosa* (root), and *Sorghum vulgare* (seed); tannin-containing fractions of *K. ixina*, *K. triandra*, and *A. villosa* and a tannin-free fraction of *K. ixina* were also used. The total extracts and the tannin-containing fractions of *K. ixina*, *K. triandra*, and *A. villosa* produced malignant fibrous histiocytomas after varying numbers of injections. The tannin-free fractions had little carcinogenicity. Generally, the tannin-containing fractions contained most of the carcinogenic material. The materials from *A. villosa* (2 mg/kg total extract and 1 mg/kg tannin-containing fractions) produced tumors in the shortest time (18 months) and were the most potent.

0714 EFFECT OF BASIC CUPRIC ACETATE ON BIOCHEMICAL CHANGES IN THE LIVER OF THE RAT

FED CARCINOGENIC AMINOAZO DYE. III. EFFECT OF COPPER COMPARED WITH SOME OTHER METALS, PHENOBARBITAL AND 3-METHYLCHOLANTHRENE ON THE METABOLISM OF 4-DIMETHYLAMINOAZOBENZENE. (E.) Yamane, Y. (Fac. Pharmaceutical Sci., Chiba U., Japan) and K. Sakai. *Chem Pharmacol Bull* 22(5):1126-1132, 1974.

Female Wistar rats were maintained for 2 weeks on diets containing copper, nickel, zinc, manganese, phenobarbital (PB), 3-methylcholanthrene (3-MC), or no additives (control group). Homogenates made from the livers of these animals were then incubated with a reaction mixture containing 4-dimethylaminoazobenzene (DAB), as were liver microsomal fractions. Copper and manganese reduced slightly the N-demethylation activity in the whole homogenate, while copper increased the ring hydroxylation activity and greatly elevated the azo reduction activity; manganese and nickel had less marked effects on the azo reduction activity, and zinc either slightly reduced or did not affect it. The elevation in the azo reduction activity increased as a function of the amount of copper in the liver homogenate. Both PB and 3-MC increased the activities of azo

reduction and N-demethylation, and PB also increased the ring hydroxylation activity. The copper-induced increases in the azo reductase and ring hydroxylase activities were positively related to the concentration of copper in the liver microsomes. The results suggest that the marked elevation in azo reductase activity in the rat liver by the concurrent administration of amino-azo dye and copper salt is a main factor in the suppression of aminoazo dye carcinogenesis.

0715 INTERACTION OF EXCITED STATES OF POLYNUCLEAR AROMATIC HYDROCARBONS WITH OXYGEN AND NITRIC OXIDE. (E.) Benson, R. (New York U., N.Y.). *Diss Abs Int B* 35(2):750-B, 1974.

0716 METABOLISM OF TETRAHYDROHOMOFOLATE (NSC 89473) IN MICE. (E.) Mishra, L. C. (Natl. Cancer Inst., Bethesda, Md.), A. S. Parmar and J. A. R. Mead. *Cancer Res* 34(5):964-967, 1974.

0717 PLACENTAL TRANSPORT OF AN ENVIRONMENTAL CARCINOGEN FOLLOWING THE INDUCTION OF ARL HYDROCARBON HYDROXYLASES. (E.) Harrison, Y. E. (Howard U., Washington, D.C.). *Diss Abs Int B* 35(1):412, 1974.

0718 EFFECT OF MUTAGENS AND CARCINOGENS ON CELLULAR TRANSFORMATION AND ACTIVATION OF VIRUSES IN VITRO. (E.) Mishra, L. (U. California, Davis). *Diss Abs Int B* 35(1):393, 1974.

0719 DISTRIBUTION OF METABOLITES OF BENZO(a)PYRENE IN THE ISOLATED PERFUSED RABBIT LUNG PREPARATION. (E.) Niemeier, R. W. (U. Cincinnati, Coll. Med., Ohio) and E. Bingham. *Toxicol Appl Pharmacol* 29(1):93-94, 1974.

0720 ATMOSPHERIC SULFUR DIOXIDE, NITROGEN DIOXIDE AND LEAD AS MUTAGENIC HAZARDS TO HUMAN HEALTH. (E.) Hickey, R. J. (Wharton Sch., U. Pennsylvania, Philadelphia), R. C. Clelland, D. E. Boyce and E. J. Bowers. *Mutat Res* 26(5):445-446, 1974.

0721 A PROPOSED HUMAN POPULATION MONITORING SYSTEM FOR ENVIRONMENTAL MUTAGENS BASED ON SOMATIC MUTATION THEORY IN CERTAIN DISEASES. (E.) Sugahara, T. (Fac. Med., Kyoto U., Japan) and A. Uyama. *Mutat Res* 26(5):438-439, 1974.

0722 MUTAGENIC EFFECT OF AFLATOXIN B₁ ON NUCLEAR AND EXTRANUCLEAR DNA IN *CHLAMYDOMONAS REINHARDII*. (E.) Schimmer, O. (Botanical Inst., U. Erlangen-Nurnberg, Germany) and R. Werner. *Mutat Res* 26(5):423-425, 1974.

0723 STUDIES OF THE CARCINOGENICITY OF AN ACETONE EXTRACT OF HASHISH. (E.) Procter, B. G. (Bio-Res. Lab., Ltd., Pointe Claire, Quebec, Canada), P. Dussault, G. Rona and C. I. Chappel. *Toxicol Appl Pharmacol* 29(1):76, 1974.

0724 INDUCTION OF TUMORS IN NON-HUMAN PRIMATES WITH VARIOUS CHEMICAL CARCINOGENS. (E.) Adamson, R. H. (Natl. Cancer Inst., Bethesda, Md.), P. Correa and D. W. Dalgard. *Toxicol Appl Pharmacol* 29(1):93, 1974.

0725 GC-MS STUDIES OF THE METABOLISM OF SAFROLE, AN HEPATOCARCINOGEN, IN THE RAT AND GUINEA PIG. (E.) Horning, M. G. (Baylor Coll. Med., Houston, Tex.), L. Bell, M. J. Carman and W. G. Stillwell. *Toxicol Appl Pharmacol* 29(1):89, 1974.

0726 AUTORADIOGRAPHIC STUDIES OF THE KIDNEYS OF HAMSTERS BEARING LONGTERM OESTROGEN IMPLANTS. (E.) Pantic, V. (Inst. Biol. Res., Beograd, Yugoslavia), J. Li and C. Villee. *Cytobiologie* 9(2):89-99, 1974.

0727 METABOLISM OF AFLATOXIN B₁ BY AN INTACT AND RECONSTITUTED RAT LIVER MICROSOMAL ENZYME SYSTEM. (E.) Nerurkar, L. S. (Virginia Polytech. Inst., Blacksburg) and T. C. Campbell. *Toxicol Appl Pharmacol* 29(1):89-90, 1974.

0728 INHALED PARTICLES. (E.) Muir, D. C. F. (Inst. Occupational Med., Edinburgh, Scotland). *Br Thorac Tuberculosis Assoc* 3(4):65-74, 1973.

0729 SOME ENZYMES OF NUCLEIC ACID METABOLISM IN PRIMARY MALIGNANT HEPATOCELLULAR CARCINOMA OF HUMANS AND IN A TRANSPLANTABLE RAT HEPATOMA INDUCED BY 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE (3'-MeDAB). (E.) Cummins, R. R. (South African Inst. Med. Res., Johannesburg), D. Balinsky, C. F. Albrecht, E. W. Geddes and I. Bersohn. *S Afr J Sci* 70(3):81-82, 1974.

0730 LIVER TUMOURS AND STEROID HORMONES. (E.) Davies, J. N. P. (Albany Med. Coll., N.Y.). *Lancet* (7856):516, 1974.

0731 DIFFERENTIAL INHIBITION BY FUCOSSES OF AGGREGATION OF RAT HEPATOMA CELLS IN ROTATION-MEDIATED CELL CULTURES. (E.) Kuroda, Y. (Natl. Inst. Genetics, Misima, Japan). *J Nat Cancer Inst* 52(1):161-166, 1974.

0732 RADIOLOGICAL DIAGNOSIS OF CROCIDOLITE INDUCED PLEURAL MESOTHELIOMATA IN THE RAT. (E.) McLachlan, M. S. F. (Welsh Natl. Sch. Med., Cardiff) and J. C. Wagner. *Br J Exp Pathol* 55(2):164-168, 1974.

0733 STUDY OF ZINC METABOLISM, LACTATE DEHYDRO-
 GENASE AND BLOOD pH IN LEUKEMIA AND LYMPHO-
MA. PRELIMINARY NOTE. (*Sp.*) Bustamante Bustamante,
J. (Fac. Med., Valladolid, Spain), M. C. Martín Mateo
and O. Ortiz Manchado. *Sangre* 18(3):271-276, 1973.

See also:

- * (Rev): 0608, 0611, 0613
- * (Viral): 0799
- * (Immun): 0855, 0872, 0879, 0880, 0913
- * (Epid-Biom): 0956, 0957, 0958, 0960

0734 LEUKEMIA IN IRRADIATED PARABIOTIC RATS. (E.) Warren, S. (New England Deaconess Hosp., Boston, Mass.), K. B. Udupa and R. N. Chute. *Radiat Res* 57(1):67-72, 1974.

Littermates of the same sex of NEDH (Slonaker derived) rats were joined in parabiosis at about 1 month of age. After 10-12 weeks in parabiosis, the right-hand partner received a single total-body x-irradiation dose of 1000 R. Parabiosis alone increased the total incidence of leukemia slightly, but significantly, over the spontaneous incidence in single rats. The irradiation of one partner reduced this elevated incidence slightly, but not to the single control level. Myeloid leukemia occurred most frequently (47%) with monocytic and lymphoid types appearing less often. The spleen was the most frequently involved organ (81%). Lymph node and liver were next, resp., in frequency. Testes were not infiltrated; ovaries occasionally were. Leukemia was shared by both partners in 61.1% of the cases. When only one had the disease, this tended to be the nonirradiated partner. When shared by both, the disease was more extensive and it is suggested that involvement of only one of the partners may indicate an early stage of the disease. Considered by sex, the male parabiatic pairs do not show a significant effect on incidence of leukemia of either parabiosis or radiation. In the females, it is hard to say whether radiation has a direct suppressing effect on hematopoietic cells or an indirect hormonal effect.

0735 ANALYSIS OF INTERPHASE CHROMOSOME DAMAGE BY MEANS OF PREMATURE CHROMOSOME CONDENSATION AFTER X- AND ULTRAVIOLET-IRRADIATION. (E.) Waldren, C. A. (Dept. Zool., U. Cambridge, England) and R. T. Johnson. *Proc Natl Acad Sci USA* 71(4): 1137-1141, 1974.

The immediate action of x-rays and ultraviolet light on the chromosomes of HeLa cells irradiated in the G1 phase of the life cycle was assessed. This assessment was made using Sendai virus-mediated fusion between mitotic and interphase mammalian cells which causes the rapid condensation of the interphase chromosomes into distinct structures, a process termed premature chromosome condensation. X-irradiation fragmented the chromosomes; but even the most finely chopped fragments retained the condensed morphology of the premature chromosome condensation of unirradiated G1 cells. For doses up to 1800 rads, the increase in the number of fragments is linearly related to the dose. One mean lethal dose (about 100 rads) yields a net increase of 10-15 fragments/G1 cell. Incubation of irradiated cells reduced the number of fragments within 2 hr, indicating a re-joining process. G1 chromosomes of cells irradiated with UV light in G1 phase were not appreciably fragmented but were elongated and attenuated so they resembled premature-chromosome-condensation chromosomes of unirradiated S-phase cells. In contrast to the immediate manifestation of damage from x-rays, the maximum induction of the "S-like" state did not occur until about 2 hr after irradiation. "S-like" chromosomes were capable of unscheduled DNA synthesis. It is suggested that the difference in chromo-

some morphology noted after UV- and x-irradiation underlies the reason why the former, but not the latter, induces unscheduled DNA synthesis in G1 cells.

0736 INFLUENCE OF GENETIC STRAIN ON THE INDUCTION OF LUNG CANCER IN HAMSTERS BY ALPHA RADIATION. (E.) Little, J. B. (Harvard U. Sch. Public Hlth, Boston, Mass.), B. N. Grossman, R. B. McGandy and W. F. O'Toole. *Eur J Cancer* 9(11/12): 825-828, 1973.

The response to multiple intratracheal instillations of the alpha emitting radionuclide polonium-210 absorbed onto hematite particles was studied in 4 inbred strains of Syrian hamsters. Each animal received 15 weekly instillations of 0.2 μ Ci ^{210}Po . Marked differences occurred among strains in their tolerance to the instillations; 2 strains gained weight, 1 remained at a steady weight, and the 4th lost weight rapidly. The frequency of tumor development was similar in all strains, but there were significant differences in tumor induction times. No differences with regard to sex were noted in either incidence or induction time. These results indicate that genetic strain does influence the response to multiple intratracheal instillations of ^{210}Po . Radiation, however, deposits its energy at random in cells, thus acting directly to initiate the carcinogenic process. It seems reasonable to expect that genetic strain will be more influential in cases of chemical carcinogenesis in which mechanisms of activation or detoxification are important factors and may come under genetic control.

0737 EFFECTS OF IONIZING RADIATION ON MAMMALIAN CELLS. (E.) Cerutti, P. A. (Dept. Biochem., U. Florida, Gainesville). *Naturwissenschaften* 61(2):51-59, 1974.

Ionizing radiation kills rapidly dividing mammalian cells with high efficiency. The radiosensitivity of rapidly dividing cells is considerably higher than that of terminally differentiated non-dividing cells, and their mode of radiation death differs. There are numerous exogenous factors which exert a radio-protecting (organic molecules containing sulfhydryl and amino groups) or radiosensitizing (molecular oxygen) effect upon mammalian cells. These agents act on a radiochemical level influencing the extent of chemical damage in the target molecule. The mode of death of rapidly-dividing mammalian cells, reproductive death, results from the loss of reproductive integrity with subsequent loss of metabolic activities and cellular functions. Nuclear DNA is the apparent major lethal target for reproductive death. The chemical damage produced by ionizing radiation in free DNA and in DNA *in situ* in the living cell has been characterized, but the products which ultimately cause cell death have not been identified. Chromosome aberrations have been implicated in radiation-induced killing. Ionizing radiation induces both chromosome aberrations and gene mutations in mammalian cells. Ionizing radiation has induced a wide variety of malignant neoplasms in mammals. The

molecular mechanism for malignant transformation by ionizing radiation remains unknown. Ionizing radiation produces at least 3 types of DNA damage: damage of the sugar-phosphate backbone leading primarily to strand breakage; damage of the heterocyclic bases; and DNA-DNA, DNA-RNA, and DNA-protein cross-links.

- 0738 BREAST CANCER AT SITE OF IMPLANTATION OF PACEMAKER GENERATOR. (E.) Zafiracopoulos, P. (Pendeli Gen Hosp., Athens, Greece) and A. Rouskas. *Lancet* (7866):1114, 1974.

Among 210 patients of an Athens hospital in whom pacemaker generators were implanted, two developed breast cancer at the site of implantation. One case involved a 63-year-old woman in whom a Vitatron demand pacemaker with epicardial electrode was implanted under the left breast. She was readmitted to the hospital 2 years later with a palpable lump at the site of implantation and probable metastases in both lung fields and the skull. The second patient was a 68-year-old woman in whom a Vitatron demand pacemaker was implanted under the right breast connected with an intracardiac electrode. Due to dysfunction of the pacemaker, a new electrode was inserted into the right ventricle 1.5 years later; at this time the generator was reimplanted under the left breast. Six months later a palpable lump was found at the site of implantation of the original pacemaker; there was no evidence of metastasis. It is possible that carcinogenesis may be related to pacing devices.

- 0739 SEDIMENTATION OF DNA FROM HUMAN FIBROBLASTS IRRADIATED WITH ULTRAVIOLET LIGHT: POSSIBLE DETECTION OF EXCISION BREAKS IN NORMAL AND REPAIR-DEFICIENT XERODERMA PIGMENTOSUM CELLS. (E.) Cleaver, J. F. (Lab. Radiobiol., U. California, San Francisco). *Radiat Res* 57(2):207-227, 1974.

Usual alkaline sucrose techniques, which produce single-stranded DNA from unirradiated mammalian cells of $2-5 \times 10^8$ daltons (120-165 S) prove inadequate for the resolution of strand breaks transiently present during the excision repair of ultraviolet (UV) damage. These breaks seem to be relatively few in number and sedimentation changes at the limit of resolution. Using a simple modification employing brief lysis in alkali, DNA with sedimentation coefficients up to 350-S have been obtained from human fibroblasts. 350-S DNA from unirradiated fibroblasts consists of complementary strands cosedimenting with choline-labeled material originating in the cytoplasm, in a conformation which allows renaturation to double-stranded DNA on neutralization after gradient fractionation. Large changes in the sedimentation coefficient occur immediately after the irradiation of normal fibroblasts with doses as low as 5-10 ergs/mm², but not xeroderma pigmentosum (XP) fibroblasts. The kinetics of the UV-induced changes in the sedimentation of DNA from normal fibroblasts are consistent with the hypothesis that they are caused by strand breaks associated with excision repair that act as

sites for strand separation in alkali. At various times after irradiation, strand breaks accumulate in DNA from XP fibroblasts, suggesting that either their cells may possess UV-specific endonucleolytic activity but lack a later stage in repair or that breaks accumulate during cell death by the action of nucleases which may be different from the repair enzymes.

- 0740 AGING IN HIROSHIMA AND NAGASAKI ATOMIC BOMB SURVIVORS. SPECULATIONS BASED UPON THE AGE-SPECIFIC MORTALITY OF PERSONS WITH MALIGNANT NEOPLASMS. (E.) Anderson, R. E. (Atomic Bomb Casualty Comm., Hiroshima, Japan), C. R. Key, T. Yamamoto and T. Thorslund. *Am J Pathol* 75(1):1-12, 1974.

The present evaluation of 1639 malignant tumors from 3067 autopsies of members of the Extended Life Span Study Sample documents displacement in age-specific mortality curve to a younger age at death from malignant neoplasms for survivors exposed to an estimated dose in excess of 99 rads. This effect is particularly pronounced in the younger age categories and among females and is not attributable to a specific neoplasm. It is postulated that the segment of the exposed population susceptible to the tumorigenic effects of radiation is also particularly sensitive to the life-shortening effects. Assuming a positive correlation between aging and the age-specific mortality of individuals with neoplasms, and neglecting the observation that the autopsy series does not identically reflect events which encompass the entire Life Span Study Sample, accelerated or precocious aging among individuals receiving the heaviest radiation would appear to continue through the 1960's and probably up to the present time.

- 0741 MAMMARY TUMORIGENESIS THROUGH IRRADIATION OF MICE. (E.) Warren, S. (New England Deaconess Hosp., Boston, Mass.) and O. Gates. *Radiat Res* 57(3):488-507, 1974.

RAP mice, possibly harboring mammary tumor virus, of representative ages were exposed to limited or lifetime whole-body continuous gamma and to fractionated x-irradiation. Doses varied from 30-2100 R and dose rates from 0.062-121R/day in the 2 series GA (ambient) and PN (perinatal) in which mammary cancer incidence was elevated. Induction of mammary cancer was related to the dose range for ovarian tumorigenesis, 30-500R, but unrelated to age when exposed. There was no statistically significant correlation between mammary cancer and ovarian tumors. Active mammary tumor virus infection was suggested by cancer-prone litters in one irradiated (PN U + SR) and one unirradiated series (OCB). Unirradiated descendants of perinatally irradiated mice with an inherited hormonal disorder had a lower incidence of mammary cancer than stock virgin mice. The data obtained in this study indicate that the induction of mammary cancer results from the interaction of many factors through systemic changes set in motion by irradiation.

0742 THYROID CARCINOMA AFTER EXPOSURE TO ATOMIC RADIATION: A CONTINUING SURVEY OF A FIXED POPULATION, HIROSHIMA AND NAGASAKI, 1958-1971. (E.) Parker, L. N. (Atomic Bomb Casualty Comm., Hiroshima, Japan), J. L. Belsky, T. Yamamoto, S. Kawamoto and R. J. Keehn. *Ann Intern Med* 80:600-604, 1974.

The incidence of thyroid carcinoma was determined among a group of persons who were proximally exposed to the atomic bomb explosions in Nagasaki and Hiroshima, and who had experienced acute symptoms of radiation exposure, a symptom-free proximally-exposed group, a more distally exposed group, and a nonexposed group. The results indicated that clinically detected thyroid carcinoma is more prevalent among individuals, particularly women, who were exposed to atomic radiation 13 to 26 years previously. A dose of 50 rads separates persons with increased relative risk of thyroid carcinoma from those at lower risk, but does not constitute a threshold dose for the condition. The relative risk is greater in both sexes among those irradiated at younger ages, but persons up to 50-years of age at the time of exposure are also at increased risk. The most common histological type of thyroid carcinoma found at autopsy was the papillary sclerosing type. Radiation thyroiditis was unrelated to the estimated atomic bomb radiation dose.

0743 EVIDENCE AGAINST A DIRECT CARCINOGENIC EFFECT ON X-RAYS *IN VITRO*. (E.) Klein, J. C. (Radiobiol. Inst., TNO, Rijswijk, Netherlands). *J Natl Cancer Inst* 52(4):1111-1116, 1974.

The carcinogenic effect of a single 300-rad dose of X-rays on cell lines derived from culture of (C57BL/Rij X CBA/Rij) F_1 mouse spleen cells was investigated. Malignant transformation, determined by tumor development in isologous mice injected s.c. with irradiated cells, was induced under conditions (e.g. low viability and high cell concentration) resulting in close contact between viable and nonviable cells, and cell debris. All tumors were fibrosarcomas with signs of active infiltrating growth, but no metastases. The same amount of cell damage caused by radiation was mechanically induced and resulted in a comparable incidence of malignant transformation. This supports the hypothesis that the carcinogenic effect of irradiation on cells is related to the presence of dead or damaged cells in close contact with viable cells; it argues against a direct carcinogenic effect of radiation on cells.

0744 POTENTIATING EFFECT OF PRIOR LOCAL IRRADIATION OF THE LUNGS ON PULMONARY METASTASES. (E.) Van Den Brenk, H. A. S. (St. Thomas's Hosp., London, England) and H. Kelly. *Br J Radiol* 47(558):332-336, 1974.

0745 RADIATION-INDUCED HEAD AND NECK TUMOURS. (E.) Gessell, T. F. (U. Texas, Hlth. Sci. Ctr., Houston). *Lancet* (7861):815-816, 1974.

0746 TRISOMY-9 IN THE BONE MARROW OF A PATIENT WITH ACUTE MYELOMONOBLASTIC LEUKAEMIA. (E.) Rutten, F. J. (Fac. Med., U. Nijmegen, Netherlands), T. W. J. Hustinx, J. M. J. C. Scheres and D. J. T. Wagener. *Br J Haematol* 26(3):391-394, 1974.

0747 CELLULAR REPOPULATION IN IRRADIATED MOUSE THYMUS AND BONE MARROW. (E.) Hiesche, K. D. (Karolinska Inst., Stockholm, Sweden) and L. Revesz. *Beitr Pathol* 151(3):304-316, 1974.

0748 POSSIBLE MECHANISMS FOR RADIATION DISTURBANCE OF TRANSCRIPTION. (E.) Umansky, S. R. (Inst. Biophys., Acad. Sci., Pushchino, USSR), B. A. Korol, Y. N. Runova and V. I. Tokarskaya. *Int J Radiat Biol* 25(1):31-41, 1974.

0749 THE EDINBURGH THOROTRAST SERIES - REPORT OF A CYTOGENETIC STUDY. (E.) Buckton, K. E. (Western Gen. Hosp., Edinburgh, Scotland) and A. O. Langlands. *Proc Third Intl Meeting Toxicity Thorotrast* (April):114-122, 1973.

0750 MEDICAL PROBLEMS CONCERNING THE CONTROL GROUP. (E.) Lorenz, D. (German Cancer Res. Ctr., Heidelberg), W. J. Lorenz and G. van Kaick. *Proc Third Intl Meeting Toxicity Thorotrast* (April):169-174, 1973.

See also:

- * (Chem): 0685
- * (Viral): 0772
- * (Epid-Biom): 0954

- 0751 CELL-FREE TRANSLATION OF MESSENGER RNA OF SIMIAN VIRUS 40: SYNTHESIS OF THE MAJOR CAPSID PROTEIN. (E.) Prives, C. L. (Dept. Biochem., Weizmann Inst. Sci., Rehovot, Israel), H. Aviv, B. M. Paterson, B. E. Roberts, S. Rozenblatt, M. Revel and E. Winocour. *Proc Natl Acad Sci USA* 71(2): 302-306, 1974.

Virus-specific RNA from BS-C-1 African green-monkey kidney cells infected with simian virus 40 was added to a sensitive cell-free translation system from wheat-germ extracts. Samples of the reaction products of protein synthesis were subjected to peptide analysis and analyzed by SDS-polyacrylamide gel electrophoresis. The poly(a)-containing RNA from the infected BS-C-1 cells directed the synthesis of a novel polypeptide that migrated in the polyacrylamide gels together with the major capsid polypeptide of simian virus 40, VP-1. The patterns of the major tryptic peptides of purified VP-1 and the novel polypeptide synthesized *in vitro* were identical after two-dimensional paper electrophoresis. The novel polypeptide was not synthesized in response to poly(a)-rich RNA from uninfected cells or from virus-infected cells treated with cytosine arabinoside. The cell-free translation of oncogenic virus mRNA, selected by hybridization, can provide the basis for identifying additional virus-specified products in permissive and transformed cells.

- 0752 ON THE ACTIVITY OF CATHEPSIN C IN HUMAN EMBRYONIC KIDNEY CELL CULTURES INFECTED WITH *HERPESVIRUS HOMINIS* (HERPES SIMPLEX). (E.) Schauer, P. (Inst. Microbiol., Med. Fac., Ljubljana, Yugoslavia), H. Hren-Vencelj and M. Likar. *Experimentia* 30(3):232-233, 1974.

Human embryonic kidney cell cultures infected with an adapted strain Z of *Herpesvirus hominis* were grown in a balanced salt solution with lactalbumin, bovine serum, penicillin, and streptomycin. The cells were homogenized and the resulting suspension along with the tissue culture fluids were assayed as enzymes. The activity of cathepsin C was increased in the infected cells and culture fluids as compared with uninfected cells. This increase was marked in the cells within 24 hours after infection. The results suggest that after herpesvirus infection, the activity of cathepsin increases first intracellularly and later in the tissue culture fluids. The results also indicate that the increase in cathepsin C activity was associated with the observed cytopathogenic changes in the infected cells. The cathepsin activity was not increased in chick embryo fibroblasts injected with *Herpesvirus hominis*.

- 0753 TUMORAL DISEASE INDUCED IN HAMSTERS BY HUMAN LEUKEMIC MATERIAL. (E.) Nastac, E. (St. S. Nicolau Inst. Virol., Bucharest, Rumania), T. Ionescu, P. Athanasia, R. Demetrescu, V. Velciu and N. Ursea. *Rev Roum Med Int* 10(4):347-350, 1973.

Four-day-old hamsters were inoculated intrasplenically with a cellular suspension prepared from the spleens and lymph nodes of humans with acute paramyeloblastic

leukemia. An s.c. tumor developing in one of these animals was excised, suspended in saline solution, and inoculated s.c. into 3-week-old hamsters. All of the animals thus treated developed tumors within 10 to 21 days of inoculation. The tumors generally appeared at the site of inoculation and adhered to the skin. The tumor-bearing animals had enlarged livers with many small tumors of the ivory-white color of the primary tumor; the spleen was seldom enlarged. Microscopically, the s.c. tumors were either lymphosarcomas or sarcomas with polymorphous cells. The liver, spleen, and lung parenchyma showed lymphocytic and lymphoblastic proliferations and, sometimes, sarcomatous polymorphous cells; in the very ectatic vasa, lymphocytes, lymphoblasts, and rare granulocytes could be seen. Immunofluorescence studies revealed a granular fluorescence in the cytoplasm of the tumoral and spleen cells, and occasionally in the liver, lung, brain, and kidney cells. This fluorescence was intense in the presence of human chronic leukemia serum, less intense and less frequent in the presence of homologous serum from tumor-bearing hamsters, and absent from normal hamster tissues. The data indicate that the hamster tumoral disease was induced by an agent present in the human leukemic material.

- 0754 RIBONUCLEIC ACID VIRUS ASSOCIATED WITH HUMAN UROTHELIAL TUMORS: SIGNIFICANCE FOR DIAGNOSIS AND TREATMENT. (E.) Fraley, E. E. (Dept. Surg., U. Minnesota, Minneapolis), A. Y. Elliot, A. E. Castro, P. Cleveland, T. Hakala and N. Stein. *J Urol* 111(3):378-381, 1974.

Transitional cell tumors of the human urinary tract obtained from 23 patients were examined for evidence of virus. Most of the tumors were grown in tissue culture, in which most grew slowly and could not be maintained past the first or second passage; the tumors in tissue culture had an epithelial appearance and bizarre morphology. The ultrafiltrates of two surgical specimens and the tumors growing in tissue culture produced a cytopathic effect in susceptible assay cells in culture. An RNA transitional cell tumor associated virus was isolated directly from two tumors and from the fluids of eight tumors in early passage tissue culture. Virus was also detected by electron microscopy in 13 tumors and tumor cells in culture. The virus resembled the RNA tumor viruses which cause tumors in animals with regard to a variety of physical and biochemical parameters. If transitional cell tumor associated virus causes transitional cell tumors, then important advances in prevention, diagnosis, and therapy are possible.

- 0755 AN ASSOCIATION BETWEEN GLOBIN MESSENGER RNA AND 60S RNA DERIVED FROM FRIEND LEUKEMIA VIRUS. (E.) Ikawa, Y. (Cancer Inst., Tokyo, Japan), J. Ross and P. Leder. *Proc Natl Acad Sci USA* 71(4):1154-1158, 1974.

A mouse cell line infected with Friend leukemia virus, T-3-C1-2, which can be induced to accumulate mouse-globin messenger RNA, was used to demonstrate

that mouse-globin messenger RNA sequences are present in viral particles purified from the culture medium of globin-producing cells. These globin messenger RNA sequences are absent from viral particles derived from T-3-C1-2 cells that are not producing globin messenger RNA. Virus-associated globin messenger RNA sequences sediment in association with the 60S viral RNA complex as well as in free, 9S form. However, under mild denaturing conditions which result in conversion of viral 60S RNA to 30S and smaller forms, all the globin sequences sediment as 9S RNA. Appropriate control experiments indicate that the virus-associated globin messenger RNA is resistant to degradation by exogenous ribonuclease; that exogenously added globin messenger RNA does not become associated with the 60S viral RNA complex; and that globin messenger RNA can be detected in virions derived from cells both induced for and constitutively synthesizing globin messenger RNA.

- 0756 BIOLOGICAL PROPERTIES OF A C-TYPE LEUKO-VIRUS ISOLATED FROM MOUSE MYELOMA CELLS. (E.) Karpas, A. (Dept. Med., U. Cambridge, England). *Eur J Cancer* 9(11/12):803-808, 1973.

A C-type virus (MMCV) was isolated in 3T3 cell culture from mouse myeloma cells but the infected cells did not transform nor did they produce abnormal proteins. MMCV acted as a helper in the rescue of murine sarcoma viral (MSV) genome from transformed non-producing mouse and hamster cells. The pseudo-type virus formed (MSV-MMCV), transformed mouse and rat cells in culture, and induced rhabdomyosarcoma when inoculated into neonatal BALB/c-mice. However, newborn mice inoculated with MMCV did not develop any tumors. MMCV shared the group specific antigen of the murine leukemia sarcoma viruses, but contained a type specific viral antigen which was not neutralized by anti-MSV-H serum. Mouse cells chronically infected with MMCV were resistant to superinfection and transformation by different pseudotypes of MSV (MSV-H, MSV-RLV, MSV-FLV and MSV-MMCV).

- 0757 ENDOGENOUS GUINEA PIG VIRUS: EQUABILITY OF VIRUS-SPECIFIC DNA IN NORMAL, LEUKEMIC, AND VIRUS-PRODUCING CELLS. (E.) Nayak, D. P. (Sch. Med., U. California, Los Angeles). *Proc Natl Acad Sci USA* 71(4):1164-1168, 1974.

The kinetics of hybrid formation between the RNA of bromodeoxyuridine-activated endogenous guinea pig virus and the DNA of leukemic, normal, or bromodeoxyuridine-activated guinea pig cells were measured by RNA-DNA hybridization in DNA excess. Results suggest that virus-specific sequences representing some 60-70% of the viral genome are unique (2-3 copies per haploid cell genome), while the remaining 30-40% are reiterated (147 copies), and that the reiterated virus-specific DNA may be composed of more than one species, each having a different reiteration frequency. No differences were found in the quantity of viral DNA sequences contained in normal, leukemic, or bromodeoxyuridine-activated guinea pig cells. These data are consistent with the contention that preexisting viral genes are activated by bromodeoxyuridine treatment. Results of

hybridization experiments done at different DNA/RNA ratios suggest that, although the virus-specific DNA is partly unique and partly reiterated, the viral RNA does not contain any detectable internal reiteration. Total mass of the viral RNA sequences is around 0.7 to 1×10^7 daltons.

- 0758 SYNTHESIS OF SIMIAN VIRUS 40 DNA IN ISO-LATED NUCLEI. (E.) Qasba, P. K. (Natl. Cancer Inst., Bethesda, Md.). *Proc Natl Acad Sci USA* 71(4):1045-1049, 1974.

Nuclei isolated from African green monkey kidney cells which were infected with simian virus 40 at different times after infection maintained *in vitro* the same temporal sequence of host and viral DNA synthesis as seen in intact cells. The viral DNA synthesized by the nuclei of cells previously infected for 32-35 hr was characterized by centrifugation through neutral and alkaline sucrose gradients, and by isopycnic banding in a propidium iodide-cesium chloride gradient. DNA synthesis in this system is maintained for only 4-5 min. Neutral sucrose gradient analysis showed that most of the radioactivity is associated with the replicative intermediate of simian virus 40 DNA and the rest sediments at 5-7 S. Alkaline gradient analysis showed that 50-60% of the radioactivity sediments as 3-7S fragments, and the rest between 7 and 16S. Pulse-chase experiments showed that in this system 3-7S fragments do not mature into long chains.

- 0759 REPLICATING DNA OF ADENOVIRUS TYPE 2. (E.) Bourgaux-Ramoisy, D. (Ctr. Hosp. U. Sherbrooke, Quebec, Canada), J. Robin and P. Bourgaux. *Can J Biochem* 52(3):181-189, 1974.

The nature of DNA synthesized in KB cells 24 hr after infection with adenovirus type 2 was investigated. Cellular DNA synthesis was strongly depressed and a new molecular form of adenovirus type 2 DNA was detected in such cells in addition to mature viral DNA. This new form, called DNA-R, is preferentially labelled after short pulses of ^3H -thymidine, while the radioactive label can be chased into mature viral DNA. The sedimentation properties of DNA-R are those expected for linear replicating molecules having 1-2 times the molecular weight of mature viral DNA. As a result of being partly single-stranded, these molecules can be separated from mature viral DNA by chromatography on benzoyleated-naphthoyleated DEAE-cellulose. Purified DNA-R was examined under the electron microscope and found to consist of Y-shaped molecules. Thus DNA-R has the properties expected for linear monomeric molecules of adenovirus type 2 DNA replicating unidirectionally.

- 0760 A DISTINCT CLASS OF INDUCIBLE MURINE TYPE-C VIRUSES THAT REPLICATES IN THE RABBIT SIRC CELL LINE. (E.) Benveniste, R. E. (Natl. Cancer Inst., Bethesda, Md.), M. M. Lieber and G. J. Todaro. *Proc Natl Acad Sci USA* 71(3):602-606, 1974.

The existence of the selectively permissive rabbit

cell line SIRC allowed definition of a new class of endogenous murine type-C virus. Continuous clonal lines of transformed cells derived from the BALB/c mouse-embryo cell line BALB/3T3 contained at least 2 distinct classes of endogenous type-C viral genomes. Spontaneously released endogenous viruses grew well on the mouse cell line NIH/3T3 (N-tropic viruses) but not on the rabbit cell line SIRC. Type-C viruses induced by 5-bromodeoxyuridine treatment grew well on SIRC (S-tropic viruses) but not in NIH/3T3 or BALB/3T3. 5-Bromodeoxyuridine-treated AKR mouse-embryo cells also released an S-tropic virus. N-tropic and S-tropic viruses both had the mouse intraspecies gs-1 and viral RNA-directed DNA polymerase antigenic determinants. DNA-RNA hybridization techniques revealed that the 2 host-range classes of endogenous viruses are only partly related to each other. Cell transformation facilitated the spontaneous release of the N-tropic viruses; treatment with thymidine analogues induced the production of the S-tropic viruses. Thus, the two classes of viral genomes appear to be subject to different cellular controls.

- 0761 C-TYPE PARTICLES IN BABOON (*PAPIO CYNOCEPHALUS*) PRE-IMPLANTATION EMBRYOS. (E.) Kalter, S. S. (Microbiol. Infectious Dis., Southwest Fdn. Res. Education., San Antonio, Tex), M. Panigel, D. C. Kraemer, R. L. Heberling, R. J. Helmke, G. C. Smith and A. Hellman. *J Natl Cancer Inst* 52(6):1927-1928, 1974.

Preimplantation baboon (*Papio cynocephalus*) embryos obtained at days 4, 5, 7, and 8 were examined by electron microscopy. In each, several immature C-type particles were observed in the zona pellucida and the perivitelline space surrounding the outer blastomeres of the embryo. Two embryos contained occasional budding and immature particles in the interblastomeric spaces. No intracellular viral types were observed. These data support the concept of a vertical transmission of oncornavirus genes.

- 0762 EFFECT OF LYMPHOID LEUKOSIS VIRUS INFECTION ON THE CELL-MEDIATED IMMUNE CAPACITY OF THE CHICKEN. (E.) Granlund, D. J. (Dept. Microbiol., Mayo Clin. Fdn., Rochester, Minn.) and R. W. Loan. *J Natl Cancer Inst* 52(4):1373-1374, 1974.

Fertile eggs from commercial White Leghorn chickens were inoculated i.v. with Rous associated virus (RAV-1) after 14 days of incubation. Inapparently infected birds as well as those with clinical signs of leukosis developed a variety of neoplasms by 32 weeks of age. Target cells (chicken red blood cells) were labeled with ^{51}Cr and incubated with splenic lymphoid cells from the virus infected chickens in the presence or absence of phytohemagglutinin (PHA-P). Clinically infected birds had a decreased cell-mediated immune capacity, as compared with controls, while the inapparently infected birds did not differ significantly from the controls. The inapparently infected group was more reactive than the group expressing clinical disease. The T-cell functions of the inapparently infected group were normal, but a

depressed T-cell function was found in the clinically diseased birds. Thus, RAV-1 did not appear to appreciably affect the T-cell population until the advanced stages of the disease.

- 0763 SPONTANEOUS DISAPPEARANCE OF TUMORIGENICITY IN A POLYOMA VIRUS-INDUCED NEOPLASM CARRIED *IN VITRO*. (E.) Cohen, J. M. (Natl. Cancer Inst., Bethesda, Md.) and L. W. Law. *Proc Soc Exp Biol Med* 145(2):385-388, 1974.

After 100 passages in tissue culture, cells of Py-89 (a polyoma-induced neoplasm in C57Bl/Ka mice) spontaneously lost their ability to cause tumors in syngeneic recipients even when 6×10^7 cells were given i.p., whereas previously as few as 10^3 cells produced tumors in 50% of syngeneic recipients. Individual cells retained their elongated fibroblastic appearance, but now grew in dense sheets, whereas they had previously grown with much piling up of cells, leaving large areas free of cells. Five weekly s.c. injections of 2×10^6 Py-8914b cells (designation of this new variant) into C57Bl/Ka mice induced transplantation resistance to challenge doses (10^4 , 10^5 , 10^6) of tumorigenic Py-89 cells. Immunized mice were protected from these challenges. Py-8914b cells specifically sensitized peritoneal exudate cells to lyse H-2^b target cells in the ^{51}Cr -release cell-mediated cytotoxicity assay, thereby demonstrating retention of their original alloantigens. Lymphocytes sensitized to polyoma-specific antigens killed Py-8914b cells in the microcytotoxicity assay, but did not kill the antigenically unrelated SSA-4 cells in 2 representative experiments. Polyoma sensitized lymphocytes significantly killed both Py-8914b and MCA 8/2 cells, but killed the former to a greater degree. Thus an apparent cross-reactivity was detected between polyoma antigens and those of the MCA 8/2 *in vitro*. Both these lines may be antigenically related to similar cells, namely mouse embryo cells, and the cross-reactivity may be recognition of embryonic membrane antigens.

- 0764 ADDITIONAL EVIDENCE OF TYPE-C PARTICLES IN HUMAN PLACENTAS. (E.) Vernon, M. L. (Microbiol. Associates, Bethesda, Md.), J. M. McMahon and J. J. Hackett. *J Natl Cancer Inst* 52(3):987-989, 1974.

Fifteen placentas from apparently normal full-term deliveries were examined by electron microscopy. Budding or free immature type-C particles were observed in 12 of these placentas. They were extremely rare but were readily distinguishable from the numerous other dense particles in the placental tissues. There is some evidence that the type-C particles may bud from mesodermal components of the chorionic villi; the particles were found in the trophoblastic epithelial layer primarily at the basal portion of the syncytiotrophoblast in areas devoid of cytotrophoblastic epithelium. The particles were approximately 90 nm in diameter with inner nucleoid components about 45 nm in diameter. The overall density of the particles was more homogeneous than that of mouse type-C particles. Reverse transcript-

(0765-0768)

ase assays performed on Moloney concentrates from five placentas were not significantly above background activity. These data tend to support the concept of a vertically transmitted genome.

0765 NORMAL HUMAN MAMMARY CELLS IN CULTURE: EVIDENCE FOR ONCORNAVIRUS-LIKE PARTICLES.

(E.) Furmanski, P. (Div. Biol. Sci., Michigan Cancer Fdn., Detroit), C. Longley, D. Fouchey, R. Rich and M. A. Rich. *J Natl Cancer Inst* 52(3):975-977, 1974.

Normal human mammary epithelial cells from a single donor were cultivated from postnursing fluids, grown in medium containing autologous serum, and labeled with ^3H -uridine. The culture supernatants were pelleted and the pellets fractionated on 20-50% sucrose gradients. Peaks of acid-precipitable radioactivity were observed in the gradient corresponding to densities of 1.16-1.19 g/cc. The same region of gradients fractionated from the supernatants of unlabeled cultures exhibited reverse transcriptase activity with 70S RNA; the cells themselves also showed enzymatic activity in the simultaneous detection test.

0766 STUDY OF THE SENSITIVITY OF LABORATORY ANIMALS AND CELL CULTURES TO LPV ONCORNAVIRUS. (Rus.) Andzhaparidze, O. G. (Moscow Sci. Res. Inst. Viral Preparations, USSR), L. G. Stepanova, V. D. Lotte, A. L. Liozner, V. P. Kuleshova and N. R. Shukhmina. *Vopr Virusol* (6):725-728, 1973.

The oncogenic activity of LPV oncornavirus, isolated from a patient with acute leukemia, was tested by injecting into newborn and adult mice (noninbred albino and BALB/c and C57Bl/6 strains), noninbred albino rats, Syrian hamsters, guinea pigs and rabbits. Newborn mice, rats, and hamsters received 0.1 ml of virus-containing solution s.c. while adults were injected with 1-3 ml s.c., i.m., i.p., and i.v. Guinea pigs received a total of 5 ml i.p. and i.m., while rabbits were given 10 ml i.v. and i.m. After two inoculations animals were observed for 12 months. The frequency with which tumors developed in these animals was not significantly different from that in controls. Antibodies to LPV oncornavirus were found in the sera of all animals. Tests for viral replication and the production of virus-specific antibodies were performed on continuous cell cultures from the Syrian hamster (BHK 21-C-13, BHK-C-7), rhesus monkey (MK2, M10), rat (FK), and mouse (1); three lines of human diploid cells (WI-38, L-58, L-63); and trypsinized cell cultures from the lungs and skin and muscle tissue of human embryos, kidneys of rhesus monkeys, and kidneys and lungs of bovine, Syrian hamster, and mouse (BALB/c) embryos. LPV oncornavirus replicated only in primary cultures of human embryonic lung and the three lines of human diploid cells. Only virus-specific antigen production occurred in inoculated cultures of human embryonic skin and muscle tissue. A study of the dynamics of viral replication in human diploid cell cultures showed that there was a correlation between the number of virus particles produced in the cells,

the transformation activity of the culture fluid, and the number of cells containing virus-specific antigen. All three of these parameters increased with time.

0767 SUBSTRATE-ATTACHED GLYCOPROTEINS FROM NORMAL AND VIRUS-TRANSFORMED CELLS. (E.)

Terry, A. H. (Case Western Reserve U., Sch. Med., Cleveland, Ohio) and L. A. Culp. *Biochemistry* 13(3):414-425, 1974.

Balb/c 3T3 mouse cells, SV40-transformed 3T3 cells (SVT2), and reverted variants of the transformed cells leave glycoproteins bound to the substrate after their removal with ethylenedis(oxyethylene-nitrilo)tetraacetic acid. The nature of this substrate-attached material was investigated. The polysaccharide component of the material from both normal and SV40-transformed cells was quantitatively glycosaminoglycan. The glycosaminoglycan is not sulfated. The polysaccharide was identified as hyaluronic acid. Filtration through Sepharose gels revealed at least 2 size classes, both containing protein and polysaccharide in ratios that differed between normal and transformed cells. Pronase digestion resulted in 3 size classes of polysaccharide - 2 with molecular weights of 10^5 - 10^6 , and a third of smaller size. Hyaluronidase digestion liberated 2 size classes of polypeptide; the minor portion was excluded from Sephadex G-50 resin, while the major portion was much smaller in size. The small polypeptide material may be covalently linked to the hyaluronic acid polysaccharide chains. The molecular composition of substrate-attached glycoproteins from normal and virus-transformed cells suggest a role for their involvement in cell-to-substrate adhesion, and possibly cell-to-cell adhesion.

0768 FAILURE TO DETECT HETEROPHILE ANTIGENS IN EPSTEIN-BARR VIRUS-INFECTED CELLS AND TO DEMONSTRATE INTERACTION OF HETEROPHILE ANTIBODIES WITH EPSTEIN-BARR VIRUS. (E.) Henle, W. (Div. Virol., Children's Hosp., Philadelphia, Pa.), G. Henle, J. Hewetson, G. Rocchi and J. Leikola. *Clin Exp Immunol* 17(2):281-286, 1974.

Serial sera from nine subjects who had been injected 10 years previously with sheep erythrocytes and who had showed heterophile antibody responses comparable to those seen in infectious mononucleosis were retrieved from storage and examined for antibodies to Epstein-Barr virus (EBV) related antigens. Eight of the subjects had preexisting antibodies to EBV as determined by neutralization tests and by indirect immunofluorescence reactions with fluorescein-conjugated antibodies to human IgG, but not with anti-human IgM conjugates. The EBV-specific reactivities remained unchanged after immunization. The results indicate that: EBV- or EBV antigen-containing lymphoblasts from carrier or freshly infected cultures contain no detectable heterophile antigen; and immunization with sheep erythrocytes does not evoke antibodies which interact with EBV or EBV-infected cells. These conclusions are supported by

the results obtained with the heterophile antibody-positive, anti-EBV-negative serum of one subject who subsequently sustained a primary EBV infection. It is unlikely, therefore, that immunization with heterophile antigen will induce immunity to infectious mononucleosis, apart from the fact that heterophile antibody responses are largely restricted to the IgM class.

0769 EFFECT OF *BRUCELLA ABORTUS* ON THE DEVELOPMENT OF RAUSCHER AND L1210 LEUKEMIA IN MICE. (Rus.) Veskova, T. K. (Inst. Exp. Clin. Oncol., Moscow, USSR), K. L. Chimishkian, and G. Ia. Svet-Moldavskii. *Vopr Virusol* (6):728-731, 1973.

Rauscher leukemia virus (RLV; 1×10^3 ID₅₀) was injected i.v. into BALB/c mice followed, 1 day later, by i.v. or i.p. injection of live or thermally inactivated *Brucella abortus* (Vaccine strain 19BA). All of these mice survived significantly longer than controls which were not infected with *Brucella* with the best results being obtained in mice injected i.p. with 2×10^9 live *Brucella*. A slight, but significant, increase in survival time occurred in the one experiment in which thermally inactivated *Brucella* were employed. Significant increases in survival time were also noted in mice injected i.v. with 2×10^8 *Brucella* one month before RLV infection, with another i.v. injection of *Brucella* being administered one day later. *Brucella* was also injected i.v. or i.p. simultaneously or 25 days before injection of leukemia L1210 cells (Ascites strain). Significantly increased survival times were obtained in 4 of the 5 experiments performed. *Brucella* may confer protection against leukemia by (1) containing or secreting substances which inhibit RLV replication or leukemia cell proliferation; (2) stimulating immunity to leukemia; (3) heterogenizing leukemia cells by previously described mechanisms; or (4) stimulating normal stem cell proliferation which is suppressed in leukemic mice.

0770 SUGAR TRANSPORT IN CHICK EMBRYO FIBROBLASTS. II. ALTERATIONS IN TRANSPORT FOLLOWING TRANSFORMATION BY A TEMPERATURE-SENSITIVE MUTANT OF THE ROUS SARCOMA VIRUS. (E.) Kletzien, R. F. (McArdle Lab. Cancer Res., U. Wisconsin Med. Ctr., Madison) and J. F. Perdue. *J Biol Chem* 249(11):3375-3382, 1974.

Chick embryo fibroblasts infected with the temperature-sensitive mutant of the Rous sarcoma virus, Ts-68, were morphologically transformed when cultured at 37 C, but retained their fusiform morphology when cultured at 41 C. Morphological transformation was accompanied by 2.5- to 4-fold increases in the rate of 2-deoxy-D-glucose uptake. Although the initial rates of 2-deoxy-D-glucose uptake and intracellular phosphorylation in Ts-68-infected fibroblasts were temperature dependent, no differences were found in the initial rates of phosphorylation in homogenates prepared from infected cells cultured at 41 and 37 C. The inhibition of 2-deoxy-D-glucose uptake by cytochalasin B was always paralleled by an equal inhibition of 2-deoxy-D-glucose

phosphorylation. Thus, transport was rate-limiting in 2-deoxy-D-glucose uptake at early time points and alterations in transport were responsible for the alterations in sugar uptake in Ts-68-infected chick embryo fibroblasts. The K_m remained constant at 2 and 5 mM at 37 and 41 C for 2-deoxy-glucose and 3-O-methyl-D-glucose, respectively, but the V_{max} was more than 2-fold greater for cells cultured at 37 C. Only the V_{max} for 2-deoxy-D-glucose transport was changed following a 6-hour shift in culture temperature from 41 to 37 C. The similar values calculated for activation energy (17.9 and 17.5 Cal/mole for the 2-deoxy-D-glucose transport reaction in Ts-68-infected cells at 41 and 37 C, respectively) are consistent with the interpretation that the increase V_{max} in cells cultured at 37 C was the result of an increase in the number of transport sites.

0771 DEXAMETHASONE STIMULATION OF MURINE MAMMARY TUMOR VIRUS EXPRESSION: A TISSUE CULTURE SOURCE OF VIRUS. (E.) Parks, W. P. (Nat'l. Cancer Inst., Bethesda, Md.), E. M. Scolnick and E. H. Kozikowski. *Science* 184(1433):158-160, 1974.

In mouse cell lines derived from mammary adenocarcinomas the synthetic steroid dexamethasone stimulated production of murine mammary tumor virus. Viral RNA and antigens were increased as much as 20-fold over basal levels. In addition, a DNA polymerase similar to the type B viral reverse transcriptase was detected in culture fluid supernatants from a permanent cell line. Further results indicated that dexamethasone stimulation of MMTV antigen production in L8A Cl 6 was accompanied by increases in MMTV RNA. These cells thus provide a possible tissue culture source of this virus and a model system for studying the mechanism of action of corticosteroids and the regulation of transcription of integrated viral DNA.

0772 CELLULAR REACTIVATION OF ULTRAVIOLET-IRRADIATED HUMAN ADENOVIRUS 2 IN NORMAL AND XERODERMA PIGMENTOSUM FIBROBLASTS. (E.) Day, R. S., III, (Nat'l. Cancer Inst., Bethesda, Md.). *Phytochem Phytobiol* 19(1):9-13, 1974.

A plaque assay for adenovirus 2 on normal human fibroblasts has been developed and used to measure the survival of ultraviolet-irradiated virus on 6 human fibroblast cell lines. When 4 xeroderma pigmentosum cell lines were used as viral hosts, an average of one lethal event per virus in the viral population was made with 10, 15, 62, and 78 J/m², resp. While using 2 normal cell lines as hosts, 197 and 205 J/m² were required to inflict the same damage. These differences are attributed to the known repair deficiency of xeroderma pigmentosum cells. The relative UV sensitivity of adenovirus growing on normal and xeroderma pigmentosum cells fits well into the general DNA repair picture provided by published data obtained with other double-stranded, nuclear-replicating DNA virus, such as SV₄₀ or herpes simplex. The advantage of this assay is that the end point is based on restoration of

total biological function to the irradiated entity, not on an arbitrary midway point generally associated with repair, such as unscheduled DNA synthesis or repair replication. However, there is a long period required for plaque formation which is an obvious disadvantage.

- 0773 LEUKEMIC MITOCHONDRIA. I. ACUTE MYELOBLASTIC LEUKEMIA. (E.) Schumacher, H. R. (Electron Microscopy Lab., Inst. Path., Harrisburg Hosp., Pa.), I. E. Szekely, S. B. Patel and D. R. Fischer. *Am J Pathol* 74(1):71-78, 1974.

Quantitative and qualitative electron microscopic studies were performed on the mitochondria of leukemic myeloblasts in three patients with myeloblastic leukemia and in three patients with myelomonoblastic leukemia. In addition, a rat embryo tissue culture infected with Moloney sarcoma virus-Moloney leukemia virus (MSV-MLV) was subjected to detailed electron microscopic examination. Significant quantitative differences between the normal and leukemia human mitochondria were not observed, although qualitative abnormalities were found in the human leukemic mitochondria and the tissue culture material. These abnormalities included variable forms of the leukemia mitochondria (twisted, tear-drop, and irregular shapes), fewer cristae, disrupted mitochondria with virus-like particles, smaller granules in greater abundance, occurrence of mitochondrial DNA fibers, and contact between the mitochondrion and nucleus. The tissue culture material revealed similar changes but showed more virus particles located outside the cells, in intracytoplasmic sacs, and within the mitochondria. In addition, the tissue culture material had two features not observed in the human material: budding from the outer mitochondrial membrane into the mitochondrial matrix; and virus particles attached to the cristae. These data indicate that viral material might be transported to the nucleus via the mitochondria.

- 0774 RNA TUMOR VIRUSES PRESENT IN GROWING AND ABSENT IN REGRESSING MAMMARY TUMORS OF MICE. (E.) Hehlmann, R. (Coll. Physicians Surgeons, Columbia U., New York, N.Y.), A. Goldfeder and S. Spiegelman. *J Natl Cancer Inst* 52(1):49-61, 1974.

Growing and regressing mammary tumors from X/Gf and DBA/212 mice were examined by light and electron microscopy and RNA-DNA hybridization and were assayed for 70S RNA and reverse transcriptase. The growing tumors showed mature type-B particles within the intracellular space, as well as budding particles from the plasma membrane and from the bordering membranes of the microvilli. Neither mature nor budding particles were detected in the spontaneously regressing tumors. Similarly 70S RNA reverse transcriptase complexes were detected at densities characteristic of RNA tumor viruses in the growing tumors: no evidence of such complexes was found in the regressing tumors. DNA-RNA hybridization studies also indicated the presence of virus-related RNA in the growing tumors, while no virus-related RNA was present in the regressing tumors. The data

suggest that the continuous presence of an RNA tumor virus may be associated with the maintenance of the malignant state of the tumor.

- 0775 POLYOMA VIRAL DNA REPLICATED AS A NUCLEO-PROTEIN COMPLEX IN CLOSE ASSOCIATION WITH THE HOST CELL CHROMATIN. (E.) Seebeck, T. (Dept. Molecular Biol., U. Geneva, Switzerland) and R. Weil. *J Virol* 13(3):567-576, 1974.

Primary mouse kidney cell cultures were infected with polyoma (Py) viral lysates, after which the cellular DNA was pulse labeled with (³H) thymidine. Two Py-specific DNA-protein complexes (A and B) were subsequently isolated from the cellular chromatin by gentle homogenization in 0.5 M NaCl. The DNA from these two complexes was characterized by velocity sedimentation under neutral and alkaline conditions, by CsCl equilibrium density gradient centrifugation in the presence or absence of ethidium bromide, and by hybridization with Py DNA I. Both complexes contained exclusively Py DNA, with complex A containing Py DNA molecules in different stages of replication and complex B containing only mature Py DNA I molecules. Both complexes are nucleoproteins with the same buoyant density (1.470 g/cm³), which suggests that newly synthesized stretches of Py DNA are immediately complexed with proteins and that the DNA:protein ratio of the complex remains unchanged throughout replication. The proteins in the A and B complexes exhibit in acrylamide gels essentially the same pattern as the small proteins present in purified Py virions. These proteins are host cells histones synthesized during Py-induced chromatin replication. Thus, replicating Py DNA appears to be immediately complexed with mouse cell histones and complex B may become the "core" of progeny Py virions. These results support the hypothesis that Py DNA uses the chromosomes replication machinery for its own synthesis and that Py-induced replication of the host cells chromatin is necessary to provide the replicating Py DNA with histones.

- 0776 C-TYPE VIRUS PARTICLES IN A REPTILIAN TUMOR. (E.) Lunger, P. D. (Dept. Biol. Sci., U. Delaware, Newark), D. W. Hardy, Jr. and H. F. Clark. *J Natl Cancer Inst* 52(4):1231-1235, 1974.

A mature female corn snake (*Elaphe guttata*) developed a small, dorsal s.c. swelling, which was excised and examined by light and thin-section electron microscopy about 1 year later. The tumor was found to be an embryonal rhabdomyosarcoma which histologically resembled this tumor type in man. Bundles of cytoplasmic filaments were occasionally seen. Budding and extracellular virus particles were associated with less than 1% of the tumor cells examined. These particles resembled the C-type viruses of avian and mammalian origin in terms of size, general architecture, and stages and site of formation (plasma and vacuolar membranes). No other type of particle was observed in this tumor. C-type virus particles were occasionally seen in the spleen of the tumor-bearing

snake but were not found in the pancreas. Particles were not found in the spleens of two tumor-free corn snakes. These data support the hypothesis that C-type viruses may have an etiologic function in poikilotherm oncogenesis.

- 0777 REVERSE TRANSCRIPTASE IN NORMAL RHESUS MONKEY PLACENTA. (E.) Mayer, R. J. (Nat. Cancer Inst., Bethesda, Md.), R. G. Smith and R. C. Gallo. *Science* 185(4154):864-867, 1974.

Particles with the morphology of type C virus have been identified from primate placentas by electron microscopy. A reverse transcriptase (RNA-dependent DNA polymerase) was isolated and purified from microsomal pellets of two fresh placentas of rhesus monkeys in the early stages of gestation. This enzyme was biochemically similar yet immunologically distinct from the reverse transcriptases of known tumorigenic type C RNA viruses isolated from primates, but was immunologically related to a reverse transcriptase isolated from a type C virus obtained from normal baboon placenta. These particles may represent endogenous viruses, and may function in the transfer of genetic information during embryogenesis.

- 0778 MECHANISMS OF GENETIC RESISTANCE TO FRIEND VIRUS LEUKEMIA IN MICE. I. ROLE OF ^{89}Sr -SENSITIVE EFFECTOR CELLS RESPONSIBLE FOR REJECTION OF BONE MARROW ALLOGRAFTS. (E.) Kumar, V. (Boston U. Sch. Med., Mass.), M. Bennett and R. J. Eckner. *J Exp Med* 139(5):1093-1109, 1974.

Adult male B6 mice were treated with ^{89}Sr , a bone-seeking isotope, using a dosage schedule known to abrogate resistance to allogeneic marrow cells. Nine days after Friend virus (FV) infection of these mice, the spleens showed malignant erythroblastosis which could not be suppressed by prior hypertransfusion, a process which suppresses physiologic erythropoiesis. The ^{89}Sr -treated mice also supported extensive virus replication, while nontreated mice did not. FV markedly suppressed the ability of the ^{89}Sr -treated B6 mice to produce antiship red blood cell (SRBC) antibodies, a feature seen normally only in genetically susceptible strains. As the dose of ^{89}Sr increased, loss of resistance to FV increased. Thus, ^{89}Sr -sensitive marrow-dependent effector (M) cells appear to mediate the genetic resistance of FV. Bone marrow cells from B10.D2 (homozygous for resistance to spleen focus-forming Friend murine leukemia virus (SFFV) mice were transplanted into previously infected and lethally irradiated DBA/2 (susceptible to SFFV) recipients which share the same hybrid histocompatibility antigens. The spleens of the DBA/2 primary recipients yielded transformed cells which were capable of producing splenic tumor colonies upon transplantation into adult, unirradiated B10.D2 secondary recipients. The tumor colonies thus induced were of B10.D2 origin. Thirty days after the transplantation of B10.D2 bone marrow cells into DBA/2 recipients, no transformed cells were detected, indicating that the B10.D2 marrow gave rise to mature M cells which resisted the

leukemic process. M cells may exert surveillance by rejecting leukemic cells and marrow transplantation from genetically resistant donors may provide a new method of treatment for leukemia.

- 0779 EVIDENCE OF SUPPRESSOR CELL ACTIVITY IN SPLEENS OF MICE BEARING PRIMARY TUMORS INDUCED BY MOLONEY SARCOMA VIRUS. (E.) Kirchner, H. (Natl. Cancer Inst., Bethesda, Md.), T. M. Chused, R. B. Herberman, H. T. Holden and D. H. Lavrin. *J Exp Med* 139(6):1473-1487, 1974.

Spleens from C57/BL/6N mice with tumors induced by the Moloney sarcoma virus (MSV) contained four times the normal number of mononuclear cells and displayed a markedly elevated mitogen-independent DNA synthesis on a per cell basis. The number of macrophages was increased 3-fold, there was a slight reduction in the percentage of T cells, the phytohemagglutinin (PHA) response on a per cell basis was decreased by about 90%, and the primary *in vitro* immune response to sheep red blood cells was suppressed by more than 90%. The PHA response was restored by purification of the MSV spleen cells in rayon adherence columns and by removal of the phagocytic cells using an iron/magnet technique. The PHA response was markedly impaired in mixtures of suppressor cells from MSV spleens and syngeneic normal spleen cells. The inhibitor cells in MSV spleens were insensitive to inactivation by anti- θ serum plus guinea pig complement (C'), but could be removed by the adherence columns and iron/magnet technique. Thus, the suppressor cells appear to belong to the monocyte/macrophage series. Evidence also indicates that the suppressor cells belong to a proliferating population in MSV spleens. Thus, a tumor, although stimulating the immune system, may suppress certain immune functions via the activation of suppressor cells.

- 0780 INDUCTION OF PARTIAL IMMUNOLOGIC TOLERANCE IN RATS AND PROGRESSIVE LOSS OF CELLULAR ANTIGENICITY IN GROSS VIRUS LYMPHOMA. (E.) Ioachim, H. L. (Dept. Path., Lenox Hill Hosp., New York, N.Y.), S. E. Keller, B. H. Dorsett and A. Pearse. *J Exp Med* 139(6):1382-1394, 1974.

Thymic lymphomas were induced in W/Fu rats via the i.p. injection of Gross lymphoma virus. Deaggregated antigen prepared from these tumors was injected i.p. into newborn W/Fu rats, which were grafted with GLV-induced thymic lymphomas or subsequent generations of transplanted lymphomas at 75-120 days of age. The Gross virus-induced lymphoma cells expressed strong virus-associated antigens and were consistently rejected when grafted in normal adult syngeneic rats. However, similar grafts were tolerated and allowed to grow progressively in rats which had been injected with the deaggregated Gross murine leukemia virus (G-MuLV) antigens. The tolerance thus produced was only partial in that the grafted lymphoma cells lost their G-MuLV membrane antigens. These cells showed an antigenic disjunction, with negative membrane and positive cytoplasmic G-MuLV antigen expression, and became transplantable in normal nonconditioned adult recipients. By further grafting, the expression of

the cytoplasmic G-MuLV antigens was similarly lost, while the lymphoma cells substantially increased their transplantability, rate of growth, and capacity for metastasis.

- 0781 PRODUCTION OF AN ONCORNAVIRUS BY THE CONTINUOUS HUMAN CELL LINE, DETROIT-6. (E.) Miller, G. G. (N. F. Gamaleva Inst. Epid. Microbiol., Moscow, USSR), V. M. Zhdanov, T. F. Lozinsky, M. Y. Volkova, K. V. Ilyin, D. B. Golubev, I. S. Irlin and A. F. Bykovsky. *J Natl Cancer Inst* 52(2):357-364, 1974.

An oncornavirus was discovered in a subline of the continuous human cell line, Detroit-6, established from bone marrow cells of a patient with lung carcinoma. Electron microscope studies of the cells revealed particles of types A and B or theta. The former were found in various parts of the cytoplasm, but the latter were predominantly in the intercellular spaces. Biochemical and biophysical tests were used to study both extracellular and intracellular virus. The extracellular virus bands at a density of 1.16-1.17 g/ml in sucrose gradients; production of such bands is inhibited by actinomycin D. The virions contains RNA with a sedimentation coefficient of 60-70S as well as slower sedimenting components, including 4S RNA. They possess the reverse transcriptase activity associated with 60-70S RNA. The virus was immunologically distinct from the mouse mammary tumor virus and shared a common antigen with the virus isolated from HEP-2 cells and with the rhesus monkey mammary carcinoma virus.

- 0782 SPECIFIC BINDING OF FACTOR(S) RELEASED BY ROUS SARCOMA VIRUS-TRANSFORMED CELLS TO SPLENOCYTES OF CHICKENS WITH ROUS SARCOMAS. (E.) Ben-Sasson, Z. (Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel), D. W. Wise and F. Doljanski. *J Natl Cancer Inst* 52(2):405-412, 1974.

Normal and Rous sarcoma virus (RSV)-transformed chicken embryo cells labeled with choline and glucosamine liberated into the culture medium molecules, presumably macromolecular membrane constituents, containing these markers. Splenocytes taken from chickens at different times after the appearance of palpable tumors (S-lymphoid cells) and bearing neoplasms of different sizes consistently exhibited a markedly greater affinity for the labeled constituents of transformed cultures than did splenocytes from normal chickens (N-lymphoid cells). The specificity of this increased binding capacity was indicated by observations that S-lymphoid cells and N-lymphoid cells did not differ in the ability to bind constituents from normal chicken embryo cultures or from cultures of unrelated cells. Preferential binding by S-lymphoid cells was also evident for labeled molecules of rat and chicken cultures transformed by B77 virus, an agent related to RSV. Specific binding was not abrogated by inactivation of the lymphoid cells with azide or cyanide. It is suggested that specific binding of target-cell membrane constituents by S-lymphoid cells represents

the first step in the development of protective cellular immune reactions.

- 0783 ULTRASTRUCTURAL COMPARISON OF PLACENTAL VIRUS WITH SEVERAL TYPE-C ONCOGENIC VIRUSES. (E.) Dalton, A. J. (Natl. Cancer Inst., Bethesda, Md.), A. Hellman, S. S. Kalter and R. J. Helmke. *J Natl Cancer Inst* 52(4):1379-1381, 1974.

An ultrastructural comparison was made between the typical type-C particles of mouse (Rauscher), cat (RD-114), gibbon ape, and baboon (M-7) tissue culture isolates and the particles associated with the syncytial trophoblast of baboon and human placenta. In all tissue culture isolates, all budding particles had the typical morphology of type-C particles with an electron-lucent space between the nucleocapsid and the envelope. In most budding particles in baboon placenta and all budding particles in human placenta, the nucleocapsid was closely applied directly to the envelope. Occasional but rare typical type-C particles were found in baboon placenta. The possibility that these kinds of type-C particles in placentas represent two different viruses is discussed.

- 0784 EFFECT OF FELINE LEUKEMIA VIRUS ON TRANSFERRED HAMSTER FETUSES. (E.) Chapman, A. L. (U. Kansas Med. Ctr., Kansas City), H. M. Weitlauf and W. Bopp. *J Natl Cancer Inst* 52(2):583-586, 1974.

Hamster blastocysts were incubated *in vitro* with a Rickard strain of feline leukemia virus (FelLV), then transferred to the uteri of recipient foster mothers. The developing fetuses were removed on day 7, 11, or 14 of pregnancy; on days 11 and 14 the embryos were classified as grossly normal fetuses or abnormal embryonic sites (i.e., moles) and examined with the electron microscope for free or budding type-C virus. Exogenous virus was taken up and replicated in the embryos. In addition, a small proportion of hamster fetuses contained endogenous type-C virus particles. Thus while 15 of 21 virus-incubated embryos had budding type-C particles on the 7th day, 3 of 21 controls incubated in FelLV-free medium also had budding virus particles. On days 11 and 14, virus particles were associated with abnormal embryonic sites but not with grossly normal fetuses. Furthermore, the proportion of embryos in the virus-treated group that developed normally to day 14 was significantly lower than in the control group. This suggested that replication of overt type-C virus may interfere with early embryonic development in the hamster.

- 0785 SYNTHESIS OF ENDOGENOUS TYPE-A VIRUS PARTICLES IN PARTHENOGENETICALLY STIMULATED MOUSE EGGS. (E.) Biczysko, W. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), D. Solter, C. Graham and H. Koprowski. *J Natl Cancer Inst* 52(2):483-489, 1974.

Parthenogenetic stimulation of normal ICR and

AKR mouse eggs induced production of type-A virus particles. Ultrastructural observations showed these virus particles in 3- to 4-celled embryos and in subsequent stages of development of these embryos in culture. Dense, granular structures in nucleoplasm and within the duplicated inner leaflet of nuclear membrane could eventually represent precursors of these type-A virus particles. Budding type-A virus particles were found in the large protrusions into the cytoplasm of the outer leaflet of nuclear membrane. Mature virus particles were in the cisternae of endoplasmic reticulum. Adjacent to the budding virus particles at the nuclear membrane were aggregates resembling the granular part of nucleoli. The production of type-A virus particles may depend on cellular RNA synthesis.

- 0786 RESCUE OF CELL-TRANSFORMING VIRUS FROM A NON-VIRUS-PRODUCING BOVINE CELL CULTURE TRANSFORMED BY FELINE SARCOMA VIRUS. (E.) Chan, E. W. (Inst. Cancer Res., Columbia U., N.Y.), P. E. Schiop-Stansly and T. E. O'Connor. *J Natl Cancer Inst* 52(2):469-472, 1974.

A fully and stably transformed but nonvirus-producing cell culture was derived from a single focus of transformed cells in a bovine embryonic trachea cell culture infected with a terminal dilution of Snyder-Theilen feline sarcoma virus (ST-FSV). However, cell-transforming virus was rescued from this nonvirus-producing culture by superinfection with feline leukemia virus (FLV, 1 ml) and by induction with 5-iodo-2'-deoxyuridine (20 µg/ml). The chemically induced virus was antigenically related to FLV but exhibited an altered host range. Unlike ST-FSV, it could no longer infect feline cells, though it was infectious for bovine and human cells.

- 0787 HETEROGENEITY OF VIRUS PRODUCTION AND ANTIGENICITY DETECTED IN CELL CLONES DERIVED FROM A "NONPRODUCER" NEOPLASM INDUCED BY MOLONEY MURINE SARCOMA VIRUS. (E.) Law, L. W. (Natl. Cancer Inst., Bethesda, Md.), K. S. S. Chang and K. Nakata. *J Natl Cancer Inst* 52(2):437-443, 1974.

Successful *in vitro* cell lines were established from a seemingly homogeneous Moloney murine sarcoma virus (M-MSV)-induced hemangiosarcoma XM-1 carried *in vivo* in syngeneic (C57BL/KaLw X C3Hf/HeLw)_{F1} mice. Most lines did not produce infectious MSV or murine leukemia virus (MuLV) *in vitro* but did acquire MuLV after passage in syngeneic hosts; MuLV of clone H-14 appeared to be of AKR (Gross) type, but all others were of Moloney type, probably representing residual virus carried in some cells but not usually detectable. Presence or absence of infectious virus did not appear to influence the immunogenicity or immunosensitivity of the clones. None contained defective MSV. All but one clone of this virally induced neoplasm possessed group-specific, cross-reacting, virus-specified transplantation antigen (VSTA). Clone H-14 was the exception and was not detectably immunogenic or immunosensitive to the rejection response of M-MSV or the clones containing VSTA.

- 0788 REPLICATING TYPE-C VIRUS PARTICLES IN MONOLAYER CELL CULTURES OF TISSUES FROM CATTLE WITH LYMPHOSARCOMA. (E.) Van Der Maaten, M. J. (Natl. Animal Dis. Ctr., Ames, Iowa), J. M. Miller and A. D. Boothe. *J Natl Cancer Inst* 52(2):491-497, 1974.

A virion with an envelope and electron-dense nucleoid, typical of the C-type viruses associated with leukemia in other species, was identified in monolayer cell cultures established from 5 of 15 cattle with lymphosarcoma. The virus particles were morphologically and antigenically identical to those previously described in lymphocyte suspension cultures from affected cattle. The filterability and infectivity of the virus particles for calves and lambs were demonstrated. Only limited quantities of virus particles were present in cell culture fluids, but the cultures could provide a useful source of material for large-scale virus concentration and purification.

- 0789 MORPHOLOGY OF "NONINFECTIOUS" SARCOMA VIRUS. (E.) Hall, W. T. (Electro-Nucleonics Lab., Inc., Bethesda, Md.), A. F. Gazdar, B. A. Hoobs and H. C. Chopra. *J Natl Cancer Inst* 52(4):1337-1343, 1974.

Two virus-producing cell culture lines, HTG2 and HTG3, were established from a transplantable hamster tumor induced by a murine sarcoma virus (MSV) after 17 and 60 *in vivo* passages, resp. HTG2 cells presumably produced only noninfectious sarcoma virions, whereas HTG3 cells yielded both sarcoma and helper viruses. Electron microscopic examination of the original virus-induced tumors, of pellets from cells grown in tissue culture, and of tissue culture medium harvested at 24, 48, 72, and 96 hr consistently revealed the same morphologic characteristics. More than 99% of the HTG2 virions retained their electron-lucent or "immature" form, in marked contrast to HTG3 virions or other typical type-C viruses, which formed electron-dense nucleoids. In addition, a large percentage of both HTG2 and HTG3 particles appeared morphologically incomplete, though completely detached or released from the cells. The inability to form dense nucleoids may be characteristic of noninfectious murine sarcoma viruses.

- 0790 INFECTIVITY OF DEOXYRIBONUCLEIC ACID EXTRACTED FROM PURIFIED NUCLEI OF CELLS NONPERMISSIVE TO ROUS SARCOMA. (Fr.) Goubin, G. (Inst. Oncol. Immunogenetics, Villejuif, France) and M. Hill. *C R Acad Sci [D] (Paris)* 278(5):685-688, 1974.

Using a modification of Marmur's method, DNA was extracted from purified nuclei of rat cells transformed by the Prague strain of Rous sarcoma virus (XC cells). The infectivity of this DNA and that extracted from whole XC cells was tested in chick fibroblast cultures. Of the 10 cultures treated with 4 µg nuclear DNA, 5 underwent transformation in contrast to 3 of 9 treated with 73.4 µg DNA ex-

tracted from whole XC cells. All of the transformed cultures contained type C virus particles. These results suggest that all of the viral DNA is present in the nucleus. The possibility that a small fraction of this viral DNA is present in the cytoplasm was ruled out by adding DNA extracted from the cytoplasmic fraction of XC cells and rat thymocytes to chick fibroblast cultures. No transformation occurred and no virus was detected.

0791 MAMMARY TUMOR VIRUS IN STRAIN GR MICE IN RELATION TO AGE AND TISSUE TYPE. (E.)

Shannon, J. M. (Cancer Res. Lab., U. California, Berkeley), B. D. Aidells and C. W. Daniel. *J Natl Cancer Inst* 52(4):1157-1160, 1974.

Normal and neoplastic mammary tissues of GR/Crgl mice were examined for the presence of mammary tumor virions. Detection of both B and cytoplasmic A particles in normal glands from mice 2 wk of age and older was the earliest reported occurrence of such particles. Virus particles were not found in normal tissue from mice 24 wk or 1 wk old. All neoplastic tissues examined had moderate or abundant virus particles. The possible relationship of these findings to the mode of viral transmission in GR mice is discussed. A portion of the latent period observed in other mammary tumor virus-infected strains, during which mature virions cannot be observed in the mammary gland, may be consigned in GR to prenatal life. Therefore, the early viral infection of GR mice and the early development of virions in normal mammary glands may be related to the early appearance of neoplastic lesions in this strain.

0792 ANTIBODY RESPONSE AND VIRUS SURVIVAL IN CATS VACCINATED AGAINST FELINE LEUKAEMIA.

(E.) Jarrett, W. (Dept. Vet. Pathol., U. Glasgow, Scotland), L. Mackey, O. Jarrett, H. Laird and C. Hood. *Nature* 248(5445):230-232, 1974.

Antibodies against feline leukemia virus (FeLV) were found in 6 of 100 young cats examined, indicating that vaccination would be valuable. In this study FeLV-infected cells were used to produce an immune response of a high level in cats. If a cat had previous experience of FeLV and had responded immunologically even to a mild degree, a secondary response occurred and no persistent infection resulted. If the virus input dose was high, the animal became infected but subsequently suppressed the infection. Cats with no previous experience of infection seemed to have a cell dose-related response. The higher doses, 2×10^9 cells, induced a good antibody level but did not terminate the infection even after a long period. The persistence of infection may have been associated with the slower rate of antibody rise (3 months) and its inability to prevent the establishment of infection of epithelial cells of many tissues. In groups given lower doses, 4×10^7 cells, the antibody rise took place in the first month and virus was not found in the animals at that time or later. The mean antibody levels achieved in these experiments are considerably higher than those in cats with naturally acquired infec-

tions. These results indicate the feasibility of vaccination against leukemia by inducing either large primary responses or small primary and large secondary responses.

0793 B-CELL CHARACTERISTICS OF HUMAN PERIPHERAL AND CORD BLOOD LYMPHOCYTES TRANSFORMED BY

EPSTEIN-BARR VIRUS. (E.) Pattengale, P. K. (Bureau Biologics, FDA, Rockville, Md.), R. W. Smith and P. Gerber. *J Natl Cancer Inst* 52(4):1081-1086, 1974.

Infection of human buffy coat leukocytes or purified cord blood lymphocytes with Epstein-Barr virus (EBV) resulted in the appearance of continuous lymphoblastoid cell lines. A high percentage of these EBV-transformed lymphoblastoid cells had B-cell characteristics, but none demonstrated T-cell markers. Furthermore, at the earliest detection of transformation, virtually all transformed lymphoblasts had B- rather than T-cell markers; thus, it was unlikely that the B-cell lines emerged because of B-cell overgrowth of T cells which had initially transformed with equal frequency. This suggested that EBV is B lymphocyte trophic *in vitro*.

0794 CARBOHYDRATE GROUPS IN THE MAJOR GLYCOPROTEIN OF ROUS SARCOMA VIRUS. (E.)

Krantz, M. J. (Dept. Biol., Johns Hopkins U., Baltimore, Md.), Y. C. Lee and P. P. Hung. *Nature* 248(5450):684-686, 1974.

The major glycoprotein component (g2) of the Bryan high-titer strain of Rous sarcoma virus RSV (RAV-1) was purified and analyzed. The results indicate that 40% (by weight) of g2 is composed of carbohydrate and that the structure of the terminal region of the carbohydrate unit consists largely of sequences: sialic acid α galactose β N-acetylglucosamine β ; and galactose β N-acetylglucosamine. g2 corresponds to the knob projections in avian RNA tumor viruses, and seems to perform an important function in that it may recognize and interact with the receptor sites of permissive host cells during the first step of successful infection. There is evidence to support the hypothesis that the carbohydrate moieties are involved during cellular interactions.

0795 EXPRESSION OF GENES FOR INTRACISTERNAL A-PARTICLE ANTIGEN IN SOMATIC CELL HYBRIDS.

(E.) Minna, J. D. (Natl. Heart Lung Inst., Bethesda, Md.), K. Leuders and E. L. Kuff. *J Natl Cancer Inst* 52(4):1211-1217, 1974.

An antigen specific for mouse intracisternal A particles was assayed by complement fixation in homogenates of cells cultured *in vitro*. Mouse neuroblastoma, fibroblast, and rat glioblastoma cell lines were characterized by clonal differences in the amount of antigen/mg cell protein. The antigen levels varied little as cells passed from the logarithmic to the stationary phase of growth. When parental mouse cell lines with high levels of antigen were fused to cells with low or undetectable levels, the

resulting hybrid clones exhibited antigen levels similar to those of the high-level parent. In control experiments, cocultivation of parental cells without induced fusion did not lead to inheritance of antigen in a previously negative line nor did fusion between two antigen-negative cells itself generate antigen production. Antigen levels were usually sustained in parental and hybrid clones and subclones over at least 40-80 cell generations. However, some hybrid clones yielded segregating subclones with lower antigen content. A-particle antigen was not detectable in 5 of 11 independent clones derived from fusion between antigen-positive mouse fibroblasts and antigen-negative rat glioblastoma cells; the basis of this variation is not known. With respect to mouse cells, the results revealed a dominant mode of inheritance for expression of A-particle antigen. Further genetic analysis of A-particle formation probably will be possible *in vitro*.

0796 MAMMALIAN SARCOMA-LEUKEMIA VIRUSES. I. INFECTION OF FELINE, BOVINE, AND HUMAN CELL CULTURES WITH SNYDER-THEILEN FELINE SARCOMA VIRUS. (E.) Chan, E. W. (Inst. Cancer Res., Columbia U., N.Y.), P. E. Schiop-Stansly and T. E. O'Connor. *J Natl Cancer Inst* 52(2):473-481, 1974.

Infection of a feline embryonic lung cell line (FEL) or a bovine embryonic trachea cell line (BET) with the Snyder-Theilen strain of feline sarcoma virus (ST-FSV) produced foci of degenerating or proliferating cells, resp., which provided a ready quantitation of a cell-transforming component in this virus stock. An excess of a second nontransforming virus, designated feline leukemia virus (FLV), in the virus stock was demonstrated by the resistance to superinfection with ST-FSV in cells infected with post-focus-inducing dilutions of ST-FSV. FLV shed by such nontransformed cells also induced resistance to superinfection with ST-FSV in other cell cultures. ST-FSV harvested from infected FEL or BET cultures gave apparent "one-hit" focus titration patterns when assayed on FEL or BET cultures, resp. However, when an ST-FSV stock was harvested from an infected FEL culture and assayed on BET cells, the focus titration pattern was defective. Co-infection of the BET cells with this ST-FSV and FLV harvested from BET, but not from FEL cells, gave an apparent "one hit" focus titration pattern. These results agree with previous findings that ST-FSV virus stocks consist of a mixture at least of a cell-transforming virus with an excess of a nontransforming virus. The apparent autonomy or defectiveness of the transforming virus appears to depend on the functional helper capacity of the FLV component in various cells.

0797 DIVERSITY OF ENVELOPE ANTIGENS ON MURINE TYPE-C RNA VIRUSES. (E.) Aoki, T. (Natl. Cancer Inst., Bethesda, Md.), R. J. Huebner, K. S. S. Chang, M. M. Sturm and M. Liu. *J Natl Cancer Inst* 52(4):1189-1197, 1974.

Murine type-C RNA viruses from various cell lines were examined by immunoelectron microscopy; a rat-

typing serum and several mouse-typing sera were used. This revealed extensive diversity of viral envelope antigens (VEAs). Accordingly, a classification of type-C viruses can be based on profiles of VEAs as follows: a) group-specific (gsVEA) - a VEA common to all type-C viruses and detectable with serum from selected autoimmune aged NZB mice; b) subgroup-specific (sub-gsVEA) antigens common to typical murine leukemia virus (MuLV), to mineral oil-induced plasmacytoma-associated type-C viruses, or to other virus populations, and detected typically with antisera to MuLV prepared in animals other than mice; c) type-specific (tsVEA) - individually specific VEA, detected with mouse antisera against type-C virus isolates or single leukemias; and d) subtype-specific (sub-tsVEA) - further subdivisions of tsVEA, indicated by VEA(s) of individual type-C viruses occasionally reacting with two or three mouse-typing sera. A single leukemia or a single cell may harbor more than one population of type-C virus identifiable by different VEA(s), and a single virus can possess two different tsVEAs, which suggests that hybrid viruses were present. Evidence supporting the proposed classification of type-C virus is detailed.

0798 ANTIGENIC RELATEDNESS OF SIMIAN-C TYPE VIRUSES. (E.) Rangan, S. R. S. (Tulane U., Delta Regional Primate Res. Ctr., Covington, La.) *Int J Cancer* 13(1):64-70, 1974.

The two simian C-type viruses, gibbon lymphoma (GLV) and simian sarcoma (SSV-1), were compared for their antigenic relatedness by serum-neutralization techniques appropriate for each virus. While GLV was neutralized completely by its homologous antiserum, its replication was merely delayed by anti-SSV-1 serum. Both anti-SSV-1 and anti-GLV antisera neutralized SSV-1 and its associated virus (SSAV-1). These results strongly indicate an antigenic relatedness of the virion envelope proteins of the two simian C-type viruses and suggest that the virion envelope proteins of SSV-1 and its associated agent are identical. The results also suggest that GLV and SSAV-1 are two noncytopathogenic C-type viruses which are antigenically related to each other but not identical; they appear to be unrelated to the feline leukemia virus.

0799 ENHANCED PRODUCTION OF MOUSE MAMMARY TUMOR VIRUS IN DEXAMETHASONE-TREATED, 5-iododeoxyuridine-STIMULATED MAMMARY TUMOR CELL CULTURES. (E.) Fine, D. L. (NCI Frederick Cancer Res. Ctr., Md.), J. K. Plowman, S. P. Kelley, L. O. Arthur and E. A. Hillman. *J Natl Cancer Inst* 52(6):1881-1886, 1974.

Medium containing 5-iododeoxyuridine (IUDR) (20 µg/ml) was added to cultures of C3H mouse-derived mammary tumor cells (Mm5mt) and left for 24 hours. An increase in virus-related RNA-dependent DNA polymerase (RDDP) activity was noted 7 days after IUDR treatment. In a second experiment, medium containing 40 µg/ml IUDR and varied concentrations of dexamethasone were added to Mm5mt cultures and left

for 24 hours; the IUDR-containing medium was then replaced with medium containing dexamethasone at the appropriate concentration. When dexamethasone was present in the growth medium and in the medium after IUDR treatment, the levels of RDDP were increased. The greatest RDDP activity was obtained with 10^{-5} M dexamethasone. Membrane immunofluorescence was also increased in the IUDR-treated cells, and further increased in the presence of dexamethasone. Membrane immunofluorescence enhancement was linear with the concentration of dexamethasone. The number of B particles produced by the Mm5mt cells was also increased by IUDR and further increased by dexamethasone, as was the production of cell-associated mouse mammary tumor virus (MMTV) antigens. These results further implicate hormones in MMTV replication and provide the basis for an *in vitro* MMTV production system.

0800 IMMUNOCHEMICAL PROCEDURE FOR PARTIAL PURIFICATION OF NEWLY SYNTHESIZED PROTEINS IN POLYOMA VIRUS-INFECTED MOUSE CELLS. (E.) Paulin, D. (Dept. Molecular Biol., Inst. Pasteur, Paris, France), J. Perreau and F. Cuzin. *J Virol* 13(3): 699-705, 1974.

A method was devised for removing a large fraction of cellular proteins from virus-infected cell extracts. The method leaves untouched and in undenatured form proteins which are made only in the infected cells. The method involves the production of a serum containing a broad spectrum of antibodies against the proteins of a given fraction from uninfected mouse cells. The serum is polymerized to form a solid phase immunoadsorbant which can be used either in columns or batchwise to remove the cellular proteins from infected cell extracts. Unadsorbed proteins, which can be either virus-induced cellular proteins or viral-coded proteins, are analyzed by polyacrylamide gel electrophoresis and autoradiography. Using this method, a broad-spectrum antiserum was obtained against nuclear proteins soluble at low ionic strength from normal 3T6 mouse fibroblasts. This antiserum was then used to remove a significant fraction of the host proteins, leading to partial purification of viral and virus-induced polypeptides from polyoma virus-infected cell extracts. Four main peptides can be selected, with molecular weights of 90,000, 70,000, 46,000, and 41,000.

0801 GENETIC EVIDENCE FOR SV40 GENE FUNCTION IN ENHANCEMENT OF REPLICATION OF HUMAN ADENOVIRUS IN SIMIAN CELLS. (E.) Kimura, G. (Tattori U. Sch. Med., Yonago, Japan). *Nature* 248(5949):590-592, 1974.

African green monkey kidney (AGMK) cells (CV-1 line) were infected with temperature-sensitive (ts) mutants of simian virus 40 (SV40) and/or human adenovirus type 2 (Ad2). The ts mutants of SV40 groups I and II enhanced the replication of Ad2 at 33-40 C. Essentially similar results were obtained using tertiary cultures of AGMK. These results indicate that the function of the SV40 virion proteins specified by cistrons I and II is not necessary for the repli-

cation of human adenovirus in simian cells. Infection by Ad2 interferes to a great extent with the replication of SV40 in simian cells. An SV40 ts mutant of complementation group III failed to enhance the replication of Ad2 at 40 C but not at 33 C in tertiary cultures. This indicates that the SV40 gene controls, either directly or indirectly, the replication of human adenovirus in simian cells. The cistron III product of SV40 may be modified by some cellular factor to enable it to carry out its function.

0802 TWO VIRUSES FROM THE LUCKÉ TUMOR ISOLATED IN A FROG PRONEPHRIC CELL LINE. (E.)

Wong, W. Y. (Dept. Biol., U. Notre Dame, Ind.) and K. S. Tweedell. *Proc Soc Exp Biol Med* 145(4):1201-1206, 1974.

The first established frog pronephric cell line was exposed to tumor cell fractions of the oncogenic (nuclear inclusion body) phase of the Lucké renal adenocarcinoma. A mixed infection of the herpes virus and adeno-like virus was obtained. The adeno-like virus isolated probably represents a 4th virus associated with the Lucké tumor. This virus is judged as an adeno-like virus because of its overall diameter 70 nm with a 35 nm core, icosahedral symmetry, solid capsomeres, and production of basophilic intranuclear inclusions. It is highly cell-associated. The rounded cell cytopathogenic effect (CPE) seen after infection resembles the CPE of other adenoviruses. This adeno-like virus has a very restricted host cell susceptibility. Attempts to infect other cell lines, *Xenopus* kidney, *Xenopus* liver, and *Rana* adult kidney were unsuccessful judging from the lack of CPE. When tested by embryonic bioassay, the original tumor fractions and the first passages of the viruses in tissue culture produced subdermal hemorrhage, turgid edema and total deaths in 3-6 weeks. In subsequent passages the adeno-like virus appeared to abort and the herpes virus predominated. This may be due to inhibition by increased proliferation of the herpes virus. Bioassay of these and later passages produced no trauma within 3 months.

0803 COLCHICINE AND VINBLASTINE INHIBIT FIBROBLAST AGGREGATION. (E.) Waddell, A. W.

(Dept. Cell Biol., U. Glasgow, Scotland), R. T. Robson and J. G. Edwards. *Nature* 248(5445):239-241, 1974.

The alkaloids colchicine and vinblastine inhibit the spontaneous aggregation of hamster fibroblasts (BHK 21) after the cells are shaken in suspension and dispersed by exposure to trypsin in the presence of EDTA. The concentrations required for inhibition are similar to those required to alter the shape of the BHK cells from fibroblast-like to epithelial-like. It appears likely that the effects of the alkaloids result from interference with the assembly of microtubules. There are three possible mechanisms by which the integrity of microtubules could modify the probability that suspended cells will adhere to one another: the microtubules may influence the state of convolution of the surface; the self-

adhesiveness of trypsinized BHK cells may require some appropriate arrangement in the surface membrane of "contact sites"; or microtubules might be involved in the transport of surface membrane, which might, in turn, be required for the cell surface to become adhesive. The latter mechanism is favored at the present time.

0804 CHANGES IN A SURFACE-LABELLED GALACTOPROTEIN AND IN GLYCOLIPID CONCENTRATIONS IN CELLS TRANSFORMED BY A TEMPERATURE-SENSITIVE POLYOMA VIRUS MUTANT. (E.) Gahmberg, C. G. (Dept. Pathobiol., U. Washington, Seattle), D. Kiehn and S.-I. Hakomori. *Nature* 248(5447):413-415, 1974.

BHK cells transformed with temperature-sensitive polyoma virus (BHKpys3 Cl 7C), those transformed with wild type polyoma virus (BHKpywt Cl 4), and their progenitory cells (BHK Cl 13) were surface labeled. A surface galactoprotein of BHK with a molecular weight of 200,000 (galactoprotein a) was not labeled in BHKpywt at 32 or 39 C, or in BHKpys3 at 32 C; it was labeled in BHKpys3 grown at 39 C. In actively growing, sparse or subconfluent BHK cells, galactoprotein a was not labeled, whereas it was labeled when growth was inhibited at the saturation density. In BHKpywt, the chemical concentration of lactosylceramide was higher than in normal BHK cells, and the concentration of trihexosylceramide was considerably reduced. The concentration of lactosylceramide was also sharply increased at 39 C, whereas the concentration of hematoside was depressed. The trihexosylceramide concentration in BHKpys3 was low at both temperatures. The results suggest that although trihexosylceramide reduction accompanies polyoma virus transformation, it is not under the control of the ts3 gene function and is not implicated in the regulation of cell growth. Increase lactosylceramide could be essential for the expression of crucial aspects of the transformed phenotype, including the regulation of growth. The galactoprotein a, lactosylceramide, and hematoside concentrations may be related to growth control in BHK cells.

0805 A COLINEAR MAP RELATING THE SIMIAN VIRUS 40 (SV40) DNA SEGMENTS OF SIX ADENOVIRUS-SV40 HYBRIDS TO THE DNA FRAGMENTS PRODUCED BY RESTRICTION ENDONUCLEASE CLEAVAGE OF SV40 DNA. (E.) Lebowitz, P. (Yale U. Sch. Med., New Haven, Conn.), T. J. Kelly, Jr., D. Nathans, T. N. H. Lee and A. M. Lewis, Jr. *Proc Natl Acad Sci USA* 71(2):441-445, 1974.

The simian virus 40 (SV) DNA segments present in a series of adenovirus-SV40 hybrids were mapped with respect to the sites of cleavage of SV40 by restriction endonucleases. Nucleic acid hybridizations were performed between equimolar quantities of the denatured DNAs of SV40 and each hybrid virus and the radio-labeled transcripts of 11 DNA fragments obtained by the cleavage of SV40 DNA by restriction endonuclease from *Hemophilus influenzae*. In a second approach, selected fragments of SV40 DNA produced by the *H. influenzae* or *H. parainfluenzae*

restriction endonucleases were used to form heteroduplex DNA molecules with adenovirus and adenovirus-SV40 hybrid DNA, which were then analyzed by electron microscopy. The two sets of data were consistent and have permitted alignment of the map of the SV40 segments of the hybrid viruses with the *H. influenzae* and *H. parainfluenzae* cleavage maps of SV40. Since cells infected with some of the hybrid viruses contain one or more SV40-specific antigens, the genetic determinants of these antigens could be localized on the cleavage map.

0806 HEMIC CELL-ASSOCIATED MAMMARY TUMOR VIRUS ACTIVITY IN BALB/cf3H MICE. (E.) Nandi, S. (Cancer Res. Lab., U. California, Berkeley), C. Helmich and S. Haslam. *J Natl Cancer Inst* 52(4):1277-1283, 1974.

Mammary tumor virus (MTV) activity in hemic cells from different sources in the Balb/cf3H mouse was studied under various experimental conditions to determine if non-nucleated reticulocytes or nucleated cells are carriers of bloodborne MTV (B-MTV). Comparisons were also made of the titer of MTV activity in hemic cells from different sources and between these cells and mammary tumor cells, which are carriers of B-type particles. Titration of B-MTV activity in blood cells of control, hemorrhagic-anemic, and hypertransfusion-induced polycythemic mice showed a lack of correlation between the numbers of circulating reticulocytes and the titer of MTV. However, the incidence of mammary nodules in polycythemic mice inoculated with mammary-tissue-borne MTV (M-MTV) was less than that of similar mice inoculated with B-MTV. Nucleated hemic cells were separated from the nonnucleated cells by selective lysis of the latter cells with NH_4Cl or by immune hemolysis followed by differential centrifugation. Such cell preparations with solely or chiefly nucleated cells nevertheless contained MTV activity. These results indicate that virus activity associated with blood is carried by the nucleated cells (leukocytes and/or hematopoietic stem cells). MTV activity was detectable in nucleated hemic cells from all sources and the titer appeared less in circulating blood cells compared with those from other sources. Thus spleen and blood cells were considered the most suitable sources for B-MTV studies. MTV activity in mammary tumor cells was at least 10 times higher than in the nucleated hemic cells. However, accurate comparison was not feasible without proper identification of the cells containing B-MTV activity.

0807 VIRUS PRODUCTIVE TRANSFORMATION OF MAR-SUPIAL CELLS BY SCHMIDT-RUPPIN STRAIN OF RSV. (E.) Svoboda, J. (Inst. Exp. Biol. Genetics, Czechoslovak Acad. Sci., Prague), L. Donner and O. Mach. *Nature* 248:503-505, 1974.

The rat-kangaroo kidney cell line PtK 1 was mixed with Brown Leghorn chicken fibroblasts (BLEF) infected with the Schmidt-Ruppin strain of Rous sarcoma virus (SR RSV); the BLEF cells were either resistance-inducing factor (RIF)-free or irradiated.

Avian gs antigen was detected in the RSPtK 1 (PtK 1 cells plus RIF-free BLEF) and RS(X)PtK 1 (PtK 1 cells plus irradiated BLEF) mixed cell cultures. Living cells from the RSPtK 1, RS(X)PtK 1, and RSPtK 1/K1 (clone derived from RSPtK 1 cells) cells gave rise to Rous sarcomas after the injection of relatively small numbers of living cells into chickens, and infectious virus was detected when chickens were injected with cell-free culture fluid collected from full-grown cell layers. The mean virus titer varied from 1.2 to 5×10^1 FFU/ml. Budding virus particles and mature C-type particles were identified by electron microscopy in the RSPtK 1 cells. When RSPtK 1 cells were grown with ^3H -uridine and the supernatant was centrifuged in 10-58% sucrose density gradients, a peak of radioactivity was detected at a density of 1.16 g cm^{-3} . The RSPtK 1 and RSPtK 1/K1 cell lines plated in soft agar and were morphologically transformed. The PtK 1 and RS(X)PtK 1 cell lines did not form colonies in soft agar and retained the epithelioid morphology, although after prolonged passages, the RS(X)PtK 1 cells did become morphologically transformed. All cell lines have eleven chromosome stemlines and the frequency of chromosome damage was not increased by RSV infection.

0808 THE ISOLATION OF SIMIAN VIRUS 40 VARIANTS WITH SPECIFICALLY ALTERED GENOMES. (E.) Brockman, W. W. (Johns Hopkins U., Sch. Med., Baltimore, Md.) and D. Nathans. *Proc Natl Acad Sci USA* 71(3):942-946, 1974.

A general method for isolating clones of simian virus 40 (SV40) variants with specifically altered DNA is described. Selective complementation with conditional mutants was used to isolate variants that could express some SV40 genes, and nonselective coinfection with wild-type virus was used to isolate variants which retained little SV40 DNA. In each case, separation of the defective variant from the "helper" virus depended on a difference in size between the two viral genomes. This difference allowed separations of the DNAs by electrophoresis in agarose and of the virions by equilibrium centrifugation in CsCl . A potential difficulty in the use of high multiplicity passage virus as a source of mutants is the possibility that several alterations of a deleted genome might be present which could affect its function. Thus, SV40 genomes containing specific deletions were constructed by excising defined segments from wild-type viral DNA, using suitable restriction endonucleases. The method described should yield variants with defections in any portion of the genome, except the regions needed for *cis* functions involved in DNA replication.

0809 RIBONUCLEASE-SENSITIVE DNA POLYMERASE ACTIVITY ASSOCIATED WITH PARTICLES DISTINCT FROM A TYPE AND C TYPE VIRAL PARTICLES IN MURINE MYELOMA TUMOR CELLS. (E.) Penit, C. (Inst. Molecular Biol., U. Paris, France), A. Paraf, F. Rougeon and F. Chapeville. *FEBS Lett* 38(2):191-196, 1974.

Myeloma MOPC 173 s.c. tumors maintained in tissue culture produced non-contact-inhibited fibroblastic

cells and contact-inhibited epithelioid cells which had lost their capacity to produce viruses and were no longer transplantable. The fibroblastic cells were grown either in suspension (MF S) or on glass surfaces (MF), while the epithelioid cells were grown only on glass surfaces (ME). Both the fibroblastic and epithelioid cells contained endogenous ribonuclease-sensitive DNA polymerase activity. Fractionation of the cells by saccharose density gradient centrifugation showed that both the MF and ME particles with the endogenous ribonuclease-sensitive activity had the same sedimentation properties. The density of these particles was 1.085, which is lower than that of the RNA tumor viruses and their precursors. Since the particulate activity was demonstrated in the non-virus-producing epithelioid cells as well as the A-type and C-type virus-producing fibroblastic cells, the presence of this activity does not appear to be related to virus production. No endogenous ribonuclease-sensitive DNA polymerase activity was detected in association with myeloma A-type and C-type viruses.

0810 BIOLOGIC CHARACTERISTICS OF TRANSFORMED RHESUS FORESKIN CELLS INFECTED WITH MASON-PFIZER MONKEY VIRUS. (E.) Fine, D. L. (Litton Bionetics, Inc., Frederick Md.), R. J. Pienta, L. B. Malan, M. T. Kubicek, D. G. Bennett, J. C. Landon, M. G. Valerio, D. M. West, D. A. Fabrizio and H. C. Chopra. *J Natl Cancer Inst* 52(4):1135-1142, 1974.

Studies, including cytogenetic, immunofluorescence, infectivity, and tumorigenicity, were conducted to characterize seven sublines of transformed rhesus foreskin cells chronically infected with Mason-Pfizer monkey virus (MPMV). These cell lines, referred to as MPfsl, released infectious MPMV and contained antigens common to MPMV-infected human lymphoblast (NC-37) and nontransformed MPMV-infected rhesus foreskin cells. Several of the MPfsl lines exhibited chromosomal changes typical of transformed cells and released interferon-like substances into the culture medium. MPfsl cells (2×10^6 viable cells) inoculated s.c. or i.p. into newborn rhesus monkeys induced palpable nodules of donor cell origin at the sites of inoculation. Although these nodules were transient, explant cultures derived from the nodule biopsy specimens continued to release infectious virus; when subsequently reinoculated into other monkeys, these cultures induced nodules. These findings provide a convenient *in vitro* system for the study of MPMV and further define the identity of MPMV as an oncornavirus.

0811 HIGH-FREQUENCY C-TYPE VIRUS INDUCTION BY INHIBITORS OF PROTEIN SYNTHESIS. (E.) Aaronson, S. A. (Natl. Cancer Inst., Bethesda, Md.) and C. Y. Dunn. *Science* 183(4123):422-424, 1974.

Chemical interference with protein synthesis was studied using BALB/3T3 and NIH/3T3 mouse cells. Chemicals included actinomycin D, cytosine arabinoside, cycloheximide, puromycin, anisomycin, sparosomycin, and mitomycin C. Each inhibitor induced C-type virus from a high percentage of cells. Pur-

omycin (10 µg/ml) activated virus from 15% of the cells, an increase more than 10^5 -fold of spontaneous frequency of virus activation. Virus activation occurred only when protein synthesis was impaired by more than 90%. At these concentrations there was associated but delayed 30-60% inhibition of both DNA and RNA synthesis. Other chemicals which inhibited RNA or DNA synthesis over a range of 30-90% but which did not inhibit protein synthesis had no detectable virus-inducing activity. The colony-forming efficiencies of cells exposed to cycloheximide, actinomycin D or cytosine arabinoside were compared. Results indicated that protein synthesis inhibitors activate virus by a mechanism involving inhibition of protein synthesis. A relatively short period of inhibition was sufficient to cause a striking induction response. That the protein synthesis inhibitors acted at a step or steps in the induction process instead of enhancing virus replication was indicated by the fact that cycloheximide caused impairment of virus production by K-BALB cells that had either been previously or newly infected with Rauscher mouse leukemia virus. In Balb/c mouse cells, protein synthesis inhibitors, unlike halogenated pyrimidines, specifically activated only BALB:virus-2, not BALB:virus 1. The study of cellular control of endogenous C-type viruses provides an opportunity for determining molecular mechanisms involved in gene regulation in eukaryotic cells.

- 0812 DNA POLYMERASE ACTIVITY FROM TWO TEMPERATURE-SENSITIVE MUTANTS OF ROUS SARCOMA VIRUS IS THERMOLABILE. (E.) Verma, I. M. (Ctr. Cancer Res., Massachusetts Inst. Tech., Cambridge), W. S. Mason, S. D. Drost and D. Baltimore. *Nature* 251(5470):27-31, 1974.

The DNA polymerase from two temperature-sensitive mutants of Rous sarcoma virus (RSV) was purified and the activities of the purified enzymes were compared with those of the DNA polymerase of wild type RSV. The results demonstrate the covariation of thermolability of the virion DNA polymerase with temperature sensitivity of infection and transformation by the virions. The two early temperature-sensitive mutants of RSV were found to have DNA polymerase more thermolabile than that of the wild type virus, while revertants of the mutants have DNA polymerase with wild type properties. This indicates that RSV RNA encodes the information for at least a part of the DNA polymerase molecule and the enzyme must be necessary to initiate infection or transformation by RSV.

- 0813 STRUCTURE OF C-TYPE VIRUS PARTICLES IN LYMPHOCYTE CULTURES OF BOVINE ORIGIN. (E.) Calafat, J. (Netherlands Cancer Inst., Amsterdam), P. C. Hageman and A. A. Rensang. *J Natl Cancer Inst* 52(4):1251-1257, 1974.

Virus particles, primarily extracellular, were observed in 14 of 15 lymphocyte cultures from cows with hyperlymphocytosis. A detailed morphologic study was done on these particles after different fixations and negative staining with phosphotungstic

acid. After glutaraldehyde and osmium fixation, the virion was roughly spherical (103 nm diameter) and enclosed in an envelope that sometimes had a high electron density and quite often had surface projections. A core of 40-90 nm diameter was central and often separated from the intermediate membrane by a translucent space. After fixation with osmium or osmium followed by uranyl acetate treatment during dehydration, the intermediate membrane was not visible and the outline of the nucleoid was fuzzy. After negative staining, the clear surface projects were 114 Å long. Two morphologic features showed that the maturation of this virus particle differed from that described for C-type particles: particles with an electron-dense, central nucleoid (like mature C-type) are still attached to the cell membrane; and no immature C-type particles are found free from the cell.

- 0814 PRODUCTION OF RNA TUMOUR VIRUS. (E.) Sottong, P. R. (Electro-Nucleonics Labs., Md.). *Process Biochem* 9(3):30-31, 1974.

Since RNA tumor viruses are not cytopathic, permanently infected virus-producing cell lines can be established and propagated as monolayer or suspension cultures. Virus recovery from the cells (which are removed from the culture media by centrifugation) is accomplished by means of a two-step density gradient procedure using zonal centrifuges. Primary virus concentration and purification is achieved using air turbine-driven continuous-flow high-speed zonal centrifuges, while a batch-type zonal rotor in an ultracentrifuge modified for zonal operation is used for secondary purification. Typical virus concentrates contain 0.3-0.8 mg protein/ml. The RNA-dependent DNA polymerase levels normally range from 2×10^6 to 1×10^7 dpm/mg of protein, using the endogenous viral ribonucleic acid as the template, and the OD 260:280 ratio averages 1.18. Virus specific antisera may be made in guinea pig and rabbits in titers of 1:64 to 1:256, making the sera as well as the antigens useful in the complement fixation tests developed for various RNA tumor viruses.

- 0815 RAPID *IN VIVO* ASSAY FOR FRIEND POLYCYTHEMIA VIRUS. (E.) Hankins, W. D. (VA Hosp., Nashville, Tenn.) and S. B. Krantz. *J Natl Cancer Inst* 52(4):1223-1229, 1974.

An assay for the Friend polycythemia virus (FVP) was developed based on the capacity of plasma from FVP-infected animals to increase greatly the splenic uptake of ^{59}Fe as early as three days after i.v. infection in fasted BALB/c mice. The increase in splenic ^{59}Fe uptake represented a proportional increase in hemoglobin synthesis, as determined by carboxymethyl cellulose chromatography of splenic homogenates from infected and control mice. Sucrose gradient experiments and hypoxia treatment confirmed, resp., that the ^{59}Fe response was not due to the presence of erythropoietin in the FVP plasma or to the induction by FVP of endogenous erythropoietin production. The ^{59}Fe assay correlated well with the spleen focus-forming assay. The assay has applicability in mon-

(0816-0828)

itoring FVP purification procedure and studying physiochemical properties of FVP.

- 0816 COMPARISON OF VIRAL MARKER PROTEINS IN MURINE LEUKEMIA VIRUS AND MOUSE UTERUS. (E.) Strickland, J. E. (Natl. Cancer Inst., Bethesda, Md.), P. D. Kind, A. K. Fowler and A. Hellman. *J Natl Cancer Inst* 52(4):1161-1165, 1974.

RNA-directed DNA polymerase and group-specific antigen were found in uteri of NIH Swiss mice in response to estrogen treatment (1 µg estradiol i.m.). The viral markers from the uterus sedimented more rapidly on glycerol gradients than did the corresponding proteins from Rauscher leukemia virus, which indicated the uterine proteins were of larger molecular wt. Template requirements of the polymerases from uterus and virus were similar, and both enzymes were inhibited by immunoglobulin G prepared against purified murine leukemia viral polymerase.

- 0817 EVIDENCE THAT THE AKR MURINE-LEUKEMIA-VIRUS GENOME IS COMPLETE IN DNA OF THE HIGH-VIRUS AKR MOUSE AND INCOMPLETE IN THE DNA OF THE "VIRUS-NEGATIVE" NIH MOUSE. (E.) Chattopadhyay, S. K. (Natl. Cancer Inst., Bethesda, Md.), D. R. Lowy, N. M. Teich, A. S. Levine and W. P. Rowe. *Proc Natl Acad Sci* 71(1):167-171, 1974.

The AKR mouse has a high titer of murine leukemia virus early in life, and virus-negative cells derived from embryos of this mouse strain can be activated to yield murine leukemia virus by treatment with 5-iododeoxyuridine. In contrast, the NIH Swiss mouse has a low leukemia incidence and no murine leukemia virus has been isolated from it (virus-negative). The difference between AKR and NIH mice has been investigated by examining the sequences specific for murine leukemia virus in nucleic acids of these mice. A single-stranded viral-DNA probe synthesized *in vitro* using murine-leukemia-virus from the AKR mouse contains at least 87% of the sequences present in the 70S viral RNA; most of these sequences are in proportions similar to their content in the 70S RNA. Using this probe in nucleic acid hybridization experiments, it was shown that NIH-mouse-cell DNA and AKR-mouse-cell DNA differ with respect to sequences specific for AKR murine-leukemia-virus: NIH mouse-cell DNA lacks some of the virus-specific sequences present in AKR-mouse-cell DNA, and there are two distinct sets of virus-specific sequences in AKR-mouse-cell DNA, whereas there is only one set in NIH-mouse-cell DNA. RNA from virus-negative AKR-mouse cells grown in tissue culture contain some, but not all, virus-specific RNA sequences; however, within 48 hr after initiating treatment of these cells with 5-iododeoxyuridine, the complete viral genome is represented in cellular RNA.

- 0818 SPLEEN CELL MITOGENIC RESPONSE IN MAREK'S DISEASE. (E.) Lu, Y. S. (Washington State U., Pullman). *Diss Abs Int B* 35(1):590-B, 1974.

- 0819 INCREASED PROTEASE LEVELS IN TRANSFORMED CELLS: A CASEIN OVERLAY ASSAY FOR THE DETECTION OF PLASMINOGEN ACTIVATOR PRODUCTION. (E.) Goldberg, A. R. (Rockefeller U., New York, N.Y.). *Cell* 2(2):95-102, 1974.

- 0820 L-ARGININE: ITS ROLE IN MAINTENANCE OF EPSTEIN-BARR VIRUS AND CONTROL OF IMMUNE PRODUCT SYNTHESIS IN BURKITT'S LYMPHOMA-DERIVED CELL LINES. (E.) Archer, D. L. (U. Maryland, College Park). *Diss Abs Int B* 35(2):947-B, 1974.

- 0821 COMPARISON OF SINGLE AND COMBINED INFECTIONS WITH LOW-VIRULENCE AND HIGH-VIRULENCE MAREK'S DISEASE VIRUS. (E.) Smith, M. W. (Cornell U., Ithaca, N.Y.). *Diss Abs Int B* 35(2):1122-B, 1974.

- 0822 THYMUS AND BONE MARROW DERIVED LYMPHOCYTE INTERACTION IN LEUKEMIA VIRUS-INFECTED MICE. (E.) Siegel, M. J. (Pennsylvania State U., University Park), W. S. Ceglowski and H. Friedman. *J Reticuloendothel Soc* 15(6):10a, 1974.

- 0823 RAPID ANALYSIS OF ONCORNAVIRAL RNA EMPLOYING AGGLUTINATION OF VIRIONS WITH CONCANAVALIN A. (E.) Stewart, M. L. (Albert Einstein Coll. Med., Bronx, N.Y.) and J. V. Maizel, Jr. *Virology* 59(2):595-599, 1974.

- 0824 STUDIES ON NUCLEIC ACIDS IN RSV-INDUCED MOUSE ASCITES SARCOMA CELLS. BASE COMPOSITIONS AND CHROMATOGRAPHIC BEHAVIORS. (E.) Yamamoto, G. (Okayama U. Med. Sch., Japan) and T. Oda. *Acta Med Odayama* 27(5/6):149-154, 1973.

- 0825 ENZYMATIC RADIOIODINATION OF THE ENVELOPE PROTEINS OF AVIAN MYELOBLASTOSIS VIRUS. (E.) Fritz, R. B. (Dept. Microbiol., Emory U., Atlanta, Ga.). *J Virol* 13(1):42-45, 1974.

- 0826 PROTEIN KINASE STIMULATED BY CYCLIC GMP IN UNINFECTED AND SIMIAN VIRUS 40-INFECTED MONKEY KIDNEY CELLS. (E.) Tan, K. B. (Wistar Inst., Philadelphia, Pa.) and F. Sokol. *J Virol* 13(1):234-236, 1974.

- 0827 CELL TRANSFORMATION MUTANTS ARE NOT SUSCEPTIBLE TO GROWTH ACTIVATION BY FIBROBLAST GROWTH FACTOR AT PERMISSIVE TEMPERATURES. (E.) Rudland, P. S. (Salk Inst. Biol. Studies, San Diego, Calif.), W. Eckhart, D. Gospodarowicz and W. Seifert. *Nature* 250(5464):337-339, 1974.

- 0828 ONCOGENIC AND TERATOGENIC EFFECTS OF VIRUSES ADMINISTERED TO HAMSTERS DURING EMBRYOGENESIS. (E.) Frankel, J. W. (Life Sci. Res. Lab., St. Petersburg, Fla.). *Teratology* 9(3):A-17, 1974.

0829 THREE-DIMENSIONAL OBSERVATION OF VIRION OF TURKEY HERPES. (E.) Okada, K. (Fac. Vet. Med., Hokkaido U., Sapporo, Japan), Y. Fujimoto, K. Yonehara, M. Onuma and T. Mikami. *J Electron Microsc* 23(2):133-135, 1974.

0830 QUANTITATION OF INDUCED MALIGNANCY IN AN *IN VITRO* SYSTEM. (E.) Alexander, J. (Poliomyelitis Res. Fdn., Johannesburg, South Africa). *S Afr J Sci* 70(3):82, 1974.

0831 FINGERPRINTS OF THE POLYPEPTIDES OF POLY-OMA VIRIONS. (E.) Fey, G. (Swiss Inst. Exp. Cancer Res., Lausanne) and B. Hirt. *Experientia* 30(6):702, 1974.

0832 EFFECT OF CHOLESTEROL AND OTHER LIPIDS ON CELL SURFACES OF TRANSFORMED AND NORMAL CELLS. (E.) Hatten, M. E. (Bioctr., U. Basel, Switzerland), A. F. Horwitz and M. M. Burger. *Experientia* 30(6):704, 1974.

0833 EPSTEIN-BARR VIRUS FROM P3HR-1 CELLS GROWN IN CHEMICALLY DEFINED MEDIUM. (E.) Nagle, S. C. (Natl. Cancer. Inst., Frederick, Md.) and B. L. Brown. *Appl Microbiol* 28(3):518-520, 1974.

0834 THE COMPLEXITY OF THE GENOME OF AVIAN TUMOR VIRUSES. (E.) Billeter, M. A. (Inst. Molec. Biol., U. Zurich, Switzerland), J. T. Parsons and J. M. Coffin. *Experientia* 30(6):700, 1974.

0835 *IN-VITRO* SYNTHESIS ON ROUS SARCOMA VIRUS RNA. (E.) Rymo, L. (Inst. Molec. Biol., U. Zurich, Switzerland), J. T. Parsons, J. M. Coffin and C. Weissmann. *Experientia* 30(6):708, 1974.

0836 C-TYPE RNA TUMOUR VIRUSES IN THE RAT AND THEIR RELATION TO THE CELL GENOME. (E.) Verwoerd, D. W. (Vet. Res. Inst., Onderstepoort, Pretoria, South Africa). *S Afr J Sci* 70(3):80, 1974.

0837 SYNTHESIS OF STRUCTURAL PROTEINS OF AVIAN RNA TUMOR VIRUSES. (E.) Vogt, V. M. (Inst. Gen. Microbiol., Bern, Switzerland) and R. Eisenman. *Experientia* 30(6):711, 1974.

0838 STUDIES ON THE SYNTHESIS OF ROUS SARCOMA VIRUS RNA *IN VIVO*. (E.) Parsons, J. T. (Inst. Molec. Biol., U. Zurich, Switzerland), J. M. Coffin, L. Rymo, R. K. Haroz and C. Weissmann. *Experientia* 30(6):707, 1974.

See also:

- * (Rev): 0611
- * (Chem): 0620, 0665, 0704, 0718
- * (Phys): 0741
- * (Imm): 0848, 0859, 0860, 0863, 0868, 0873, 0878, 0879, 0888, 0889, 0890, 0894, 0901, 0902, 0906, 0910, 0930
- * (Path): 0945

0839 IMMUNE REACTIONS IN CHRONIC MYELOID LEUKEMIA. (E.) Danieli, G. (IInd Inst. Med. Path., U. Bologna, Italy), M. Montroni and L. Magelli. *Haematologica* 57(11):697-707, 1973.

Immunoadherence and membrane immunofluorescence were used to study possible alterations of humoral immunity in 27 patients with chronic myeloid leukemia (CML), four patients with blastic crisis (BC), and seven patients with acute myeloblastic leukemia (AML). Antileukemic leukocyte antibodies were found in 52% of the CML patients by immune adherence and in 64% of the CML patients by membrane immunofluorescence. The other CML patients and the BC and AML patients failed to show an abnormal incidence of anti-leukemia cell antibodies. There was no significant correlation between the patients' immune reaction and age, sex, or immunoglobulin content. The antibodies were specific for leukemic cells and were not reactive with normal leukocytes. Moreover, the sera of the serum-positive patients cross reacted with the leukemic cells of the serum-negative patients. The presence of antibodies appeared to be correlated with the presence and number of blast cells in the peripheral blood.

0840 EXPRESSION OF DIFFERENTIATED FUNCTIONS IN HEPATOMA CELL HYBRIDS: HIGH FREQUENCY OF INDUCTION OF MOUSE ALBUMIN PRODUCTION IN RAT HEPATOMA-MOUSE LYMPHOBLAST HYBRIDS. (E.) Malawista, S. E. (Ctr. Molecular Genetics, C.N.R.S., Gif-sur-Yvette, France) and M. C. Weiss. *Proc Natl Acad Sci USA* 71(3):927-931, 1974.

The production of serum albumin was studied in somatic hybrids between well-differentiated 2s and 1s rat hepatoma cells (Faza), which produce serum albumin, and sub-diploid mouse leukemic lymphoblasts (Lc), which do not produce albumin. All of the identifiable 2s hepatoma X mouse leukemic lymphoblast hybrids (Lc2F) produced both rat serum albumin (RSA) and mouse serum albumin (MSA), with five of the 12 clones secreting albumin in amounts roughly comparable to that produced by the 2s Faza parental cells, and the other seven producing less than the parental strain. In all cases but one, roughly equal amounts of RSA and MSA were produced. All of the hybrids from the 1s cross (LcF) also produced one or both of the albumins, but RSA was not detectable in two of the clones. One of the clones produced only RSA. With one exception, none of the LcF hybrids secreted as much albumin as the Faza parent. The karyotypes of the Lc2F hybrids were extremely variable, and most failed to show clear modes. The LcF hybrid clones showed less karyotypic heterogeneity, but the modes tended to be weak.

0841 IMMUNOHISTOCHEMICAL DEMONSTRATION OF IgG IN REED-STERNBERG AND OTHER CELLS IN HODGKIN'S DISEASE. (E.) Garvin, A. J. (Med. U. South Carolina, Charleston), S. S. Spicer, R. T. Parmlay and A. M. Munster. *J Exp Med* 139(5):1077-1083, 1974.

The cytochemical localization of immunoglobulins

by means of an immunoglobulin-peroxidase bridge procedure was used to localize IgG-producing cells in spleen and lymph node specimens from a patient with Hodgkin's disease. Spleen and lymph node samples fixed lightly for optimal immunocytochemistry or processed routinely for surgical diagnosis showed strong selective immunostaining for IgG in numerous immunocytes from tumor-free areas. In addition, the Reed-Sternberg cells showed strong immunostaining for IgG but not IgM and the Hodgkin cells showed faint to strong staining for IgG. Ultrastructurally, the Reed-Sternberg and Hodgkin cells displayed abundant polyribosomes and sparse granular reticulum and appeared to form unexportable IgG on unbound ribosomes. The immunostaining technique could be of diagnostic value in the differentiation of benign hyperplasia and other neoplasms from Hodgkin's disease.

0842 PLASMA CARCINOEMBRYONIC ANTIGEN IN RENAL CELL CARCINOMA PATIENTS. (E.) Chu, T. M. (Roswell Pk. Mem. Inst., Buffalo, N.Y.), S. K. Shukla, A. O. Mittleman and G. P. Murphy. *J Urol* 111(6):742-744, 1974.

Plasma carcinoembryonic antigen (CEA) levels in 23 patients (3 women, 20 men) with advanced renal cell carcinoma were studied. Nephrectomy was performed in 21 cases, in 18 of which metastases to the bone and/or lung were found. Only one of the three patients without metastasis had slightly elevated CEA values, while CEA levels were elevated in seven of eight patients with metastasis and four of 12 patients with local recurrence and/or distant metastasis following nephrectomy. Thus, 56% of the patients had CEA values greater than 2.5 ng/ml. Following clinically successful nephrectomy or chemotherapy (with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea), the plasma CEA values tended to decrease from an elevated pretreatment level to a normal level. Thus, the CEA assay in its present form is a valuable tool in the evaluation and follow up of patients with renal cell carcinoma.

0843 URINARY CARCINOEMBRYONIC-LIKE ANTIGEN LEVELS IN PATIENTS WITH BLADDER CARCINOMA. (E.) Guinan, P. (Dept. Urol., Cook County Hosp., Chicago, Ill.), T. John, N. Sadoughi, R. J. Albin and I. Bush. *J Urol* 111(3):350-352, 1974.

Urine samples were obtained from 24 patients who had, had previously had, or were being treated for bladder carcinoma and from 27 normal controls. The mean carcinoembryonic antigen (CEA) levels in the normal urine was 2.3 ng/cc. The mean CEA level in the urine taken from bladders with active tumor was 12.3 ng/cc, while the mean CEA levels of samples taken from currently disease-free bladders was 4.3 ng/cc; the difference between the samples from the cancerous bladders and the currently disease free bladders was significant. The samples from the cancerous bladders with low stage lesions had a mean CEA level of 5.8 ng/cc, while those from cancerous bladders with high stage lesions had a mean CEA level of 14.7 ng/cc; the difference between these

two means was significant. Among the samples from the cancerous bladders, those from bladders with lesions greater than 5 gm in mass had significantly higher CEA levels than those from bladders with lesions less than 5 gm in mass. Samples taken from bladders with lesions of greater than 5 cm² in surface area had significantly higher CEA levels than those taken from bladders with lesions of less than 5 cm² in surface area. Infected urine had a higher mean CEA level than sterile urine, but the difference was less than the difference in urine CEA levels between bladders with and without cancer. Urine samples from patients with post-therapy ileal loops had significantly higher CEA levels than samples from normal controls and patients with active tumors. Urine CEA is a potentially valuable test in the diagnosis of urothelial cancer.

- 0844 PRELIMINARY STUDIES ON ANTIGENICITY OF CHRONIC LYMPHATIC LEUKEMIA CELLS IN HUMANS. (E.) Harlozinska, A. (Polish Acad. Sci., Wroclaw), S. Kotlarek-Haus, R. Richter and W. Brodzka. *Arch Immunol Ther Exp (Warsz)* 21:403-415, 1973.

Cells from patients with chronic lymphatic leukemia (CLL), chronic granulocyte leukemia (CGL), and acute myeloid leukemia (AML) and leukocytes from healthy blood donors and patients with acute inflammatory conditions were studied by means of the cytotoxic test and the indirect immunofluorescence test on living cells. Using specific immune globulins, a large number of cross reactions were performed using various target cells. The results demonstrated the presence of specific antigens on the surface of the CLL cells which were absent from the normal leukocytes of healthy blood donors belonging to different blood groups. Antileukemia immune globulins after specific absorption reacted exclusively with leukemic cells and lost the capacity for reacting with normal cells. The reaction with leukemic cells was removed by absorption of the immune serum with pooled CLL cells. The specific globulin against lymphatic leukemia cells did not cross react with leukemia cells of other types, except in some cases of AML. Antigenic specificity similar to that shown by the CLL leukocytes was observed in comparative tests with CML cells and inflammatory leukocytes.

- 0845 A MARKED SEX DIFFERENCE IN THE IMMUNIZATION CAPABILITY OF HAMSTERS TOWARDS A MOUSE TUMOUR. (E.) Kinsky, R. G. (Ctr. Immunopath. Immunol. Exp., I.N.S.E.R.M., Paris, France). *Ann Immunol (Inst Pasteur)* 125 C(3):439-443, 1974.

Male and female hamsters were immunized with lyophilized Sa I tumor cells (indigenous to the A/Jax mouse strain) via a series of six i.p. injections at 10-day intervals. Serum obtained after the last injection was incubated with A/Jax mouse erythrocytes suspended in absorbed human serum. Positive hemagglutinating reactions were regularly observed, the hemagglutinins appearing to be strictly related to the specific Sa I immunization. Three days after the last Sa I injection, the immunized hamsters were grafted s.c. with living Sa I cells. Pretreat-

ment with the lyophilized Sa I cells markedly depressed the growth of the living cells in the females, both tumor rejection and antibody production being significantly more pronounced in the females than in the males. The data show a relationship between the growth of implanted tumors and the hemagglutination response and indicate that there is a sex linked difference in the responses of the primed animals.

- 0846 CARCINOEMBRYONIC ANTIGEN: REPORT OF A SCREENING STUDY. (E.) Costanza, M. E. (Tufts-New England Med. Ctr. Hosp., Boston, Mass.), S. Das, L. Nathanson, A. Rule and R. S. Schwartz. *Cancer* 33(2):583-590, 1974.

Originally described as a specific marker for colonic carcinomas, carcinoembryonic antigen (CEA) has been found in elevated titers in patients with a variety of nonneoplastic diseases, particularly serious metabolic disorders and inflammatory bowel disease. Plasma CEA determinations were made in 553 noncancer patients undergoing barium enema examination and in 205 patients with various types of cancer. Ninety-eight of the noncancer patients had elevated CEA values, but in only 18 were these greater than 5 ng/cc. Forty-six of the CEA-positive noncancer patients had acute inflammatory bowel disease, acute gastrointestinal disorders, collagen diseases, or serious chronic metabolic diseases. Repeat CEA sampling in a third of the "false" positive groups produced normal results in most. Only 1 of the 98 "false" positive group developed diagnosable cancer within the following year. Of the CEA negative group, none have developed cancer. Among 23 patients with primary or recurrent colonic cancers, CEA radioimmunoassays were positive in 18 and greater than 5 ng/cc in 15. However, in 4 of 13 early stage colonic carcinomas, CEA values were normal. Among 27 patients who had undergone "curative" resection for colonic carcinoma but who were free of recurrent disease, seven had elevated CEA values; of these, four had values greater than 5 ng/cc. The rate of CEA positivity among other cancer patients varied from 18% to 75%; with many tumors, the positivity rate was greater when the disease was metastatic. Caution is advised in interpreting a single elevated CEA value as synonymous with colonic cancer and in dismissing the possibility of early colonic cancer in the face of a normal CEA value.

- 0847 MORPHOLOGIC EVIDENCE SUGGESTIVE OF HOST-TUMOR CELL INTERACTIONS IN VIVO IN HUMAN CANCER PATIENTS. (E.) Sulitzeanu, D. (Lautenberg Ctr. Gen. Tumor Immunol., Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel), Y. Gorsky, S. Paglin and D. Weiss. *J Natl Cancer Inst* 52(2):603-604, 1974.

Aggregates of lymphoreticular cells were observed in some pleural and ascites effusions of patients with malignant diseases. These clusters consisted of central neoplastic cells surrounded by varied numbers of lymphocytes, blastoid forms, macrophages,

and eosinophils. The clusters did not disintegrate even after several washings. Occasionally the entire cluster consisted of obviously damaged cells. Effusions displaying cluster formation in various degrees were found in about 30% of the samples examined. These clusters may be a manifestation of the immune reactivity of the patient against the tumor.

- 0848 FAILURE TO DETECT, IN HUMAN SERA, ANTI-BODIES CROSS-REACTIVE WITH GROUP-SPECIFIC ANTIGENS OF MURINE LEUKEMIA VIRUS. (E.) Charman, H. P. (U. Southern California, Los Angeles), N. Kim, M. White and R. V. Gliden. *J Natl Cancer Inst* 52(5): 1409-1413, 1974.

The sera of 25 adult cancer patients and controls, 52 children with various neoplasms, 20 juvenile patients with connective tissue disorders, and 31 healthy laboratory workers potentially exposed to RNA tumor viruses were screened in sensitive radio-immunoassays for antibodies cross-reacting with highly purified group-specific antigen of murine leukemia virus (p30). In no case were antibodies to the murine gs antigen found.

- 0849 ANAHORMONE CHIMERAS. CONJUGATES OF MELANOCYTE-STIMULATING HORMONE (MSH) FROM THE PITUITARY AND ANTIGENS FROM HUMAN MELANOMAS. (Rus.) Bershtein, L. M. (N. N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR), S. V. Potokin, L. M. Khachatryan, V. N. Golubev and V. M. Dil'man. *Dokl Akad Nauk SSR* 216(6):1402-1405, 1974.

Soluble and cellular antigens were prepared from melanomas removed from 17 patients at surgery and were conjugated with melanin-stimulating hormone (MSH) from swine pituitary. Soluble antigen in the supernatant of a water-salt extract of the tumor was incubated with MSH and methyl-p-toluenesulfonate-1-cyclohexyl-3(2-morpholinyl(4)ethyl)carbodiimide for 30 min and the reaction mixture was dialyzed against distilled water at 4 C for 96-120 hr. Cellular antigen in trypsinized melanoma cells was shaken with MSH dissolved in 0.4 M phosphate buffer (pH 7.4) and bis-diazobenzidine for 10 min at room temperature. The mixture was then allowed to stand overnight at 4 C so that the dark brown flocculent product could precipitate. *In vitro* and *in vivo* skin tests on *Rana temporaria* showed that conjugates of MSH with both soluble and cellular melanoma antigens had little or no melanophore activity. Measurements of blood levels of nonesterified fatty acids in rabbits demonstrated that neither conjugate had any lipolytic activity at the doses tested. However, the conjugate of MSH with soluble melanoma antigen inhibited the reaction of MSH with immune sera. Immunization of rabbits with the conjugates produced antibodies to MSH, melanoma antigen, and the conjugates. Immune sera for the conjugates inhibited both the melanophore and lipolytic activity of MSH to a certain extent. Thus, conjugates of MSH with soluble and cellular melanoma antigens retain their antigenic properties but lose most of the hormonal activity of MSH. It is suggested that

these conjugates might be useful in the treatment of melanomas.

- 0850 TUMOR RESISTANCE IN RATS IMMUNIZED TO FETAL TISSUES. (E.) Grant, J. P. (Nat'l. Cancer Inst., Bethesda, Md.) and S. A. Wells, Jr. *J Surg Res* 16(5):533-540, 1974.

Inbred Fischer 344/N rats were immunized with irradiated cells of either a methylcholanthrene-induced syngeneic fibrosarcoma (MCA-R), syngeneic second trimester fetal tissue, or allogeneic Marshall 520 splenic lymphocytes. Animals injected intradermally with soluble antigen extracts (SAE) of MCA-R and normal Fischer 344/N tissues were evaluated for the development of delayed cutaneous hypersensitivity reactions (DCHR). Fischer rats immune to allogeneic tissue gave no positive DCHR to either SAE. Ten of 11 rats immune to MCA-R and six of nine immune to second trimester fetal tissue gave positive reactions to MCA-R SAE but none to normal tissue SAE. In a second experiment, immunized rats were challenged subcutaneously with viable MCA-R tumor cells. Significant resistance to tumor growth was demonstrated in animals immune to MCA-R and in animals immune to second trimester fetal tissue. This resistance was unrelated to sex. Immunological similarity between fetal antigens and tumor associated transplantation antigens is suggested.

- 0851 ELECTROPHORESIS OF LYMPHOCYTES FROM NORMAL HUMAN SUBJECTS AND PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA. (E.) Goldstone, A. H. (Immunol. Labs., Edinburgh, Scotland), S. J. Urbaniak and W. J. Irvine. *Clin Exp Immunol* 17(1):113-120, 1974.

The electrophoretic mobility (EM) of peripheral blood lymphocytes from 12 normal subjects and four patients with chronic lymphocytic leukemia (CLL) was studied in relation to the thymus-derived (T) lymphocytes and bone marrow-derived (B) lymphocytic system. The electrophoretic results were compared with those obtained using the formation of sheep red blood cell rosettes, the formation of erythrocyte-antibody-complement (EAC') rosettes, and by staining for surface immunoglobulin. In the normal subjects, the majority of cells migrated quickly with a small 'tail' of slower cells. The faster populations appeared to have been T cells and the slower populations B cells. In CLL, the majority of the cells were slow migrators. There was good agreement between the percentage of fast cells as assessed by electrophoresis with that of T cells by sheep-cell rosetting; there was also some agreement between the percentage of electrophoretically slow cells to B cells by EAC' rosettes or surface immunoglobulin. It was possible to remove some of the B cells by density centrifugation after forming EAC' rosettes. This further defined the T cell peak on electrophoresis. It appears that T and B cells carry different surface charge densities which permit them to be separated by electrophoresis and that the malignant B lymphocytes of CLL migrate electrophoretically in a fashion similar to that of normal B cells.

- 0852 PASSIVE IMMUNITY AGAINST CHILDHOOD CANCER.
(E.) Lowry, W. S. (Maine Med. Ctr., Portland). *Lancet* (7858):602-603, 1974.

Most of the common forms of childhood cancer are either very rare in infancy or, if they occur in early life, have a much better prognosis than in older children. Age versus incidence data suggest that the delayed onset of neoplasia may be attributable to passive immunological factors which keep some forms of malignant disease at bay in early life, while age versus prognosis data indicate that there is some factor operating during infancy which suppresses or retards the growth of malignant disease. While Wilms' tumor and malignant melanoma in young infants appear to differ from the same diseases in older children, the different forms may represent the same tumor in different hosts. With regard to Burkitt's lymphoma and leukemia, there is some evidence that the incidence is inversely related to breast-feeding. The extreme radiosensitivity of many malignant tumors in infancy suggests that the results of radiation therapy are in some way enhanced in early life. There is also strong evidence that antibodies play a role in the prevention of malignancy. Thus, the reduced incidence of cancer in infants may be due to immunological factors; in infancy such factors are more likely to be associated with passive rather than active immunity.

- 0853 IMMUNOLOGIC STUDIES OF GLYCOPROTEINS ISOLATED FROM CELL MEMBRANES OF HUMAN LUNG CARCINOMAS. (E.) Tillack, T. W. (Washington U. Sch. Med., St. Louis, Mo.), J. Rosai and D. J. Vervynck. *J Natl Cancer Inst* 52(4):1059-1067, 1974.

Lithium diiodosalicylate was used to isolate glycoproteins from microsomal preparations of human lung carcinomas and from normal human lung tissue. A glycoprotein present in the extracts of all but one of five oat-cell lung carcinomas was identical to carcinoembryonic antigen (CEA) by Ouchterlony immunodiffusion analysis. Extracts of 11 epidermoid lung carcinomas contained antigens either identical to or cross-reacting with CEA by immunodiffusion analysis; and extracts from each of two lung adenocarcinomas had antigens that cross-reacted with CEA. Although CEA appeared to have at least one antigenic determinant not present in the cross-reacting glycoprotein from some epidermoid carcinomas, adenocarcinomas, and normal lungs, glycoproteins from the lung tumors and normal lung did not have any detectable antigenic determinants not found on CEA. No membrane glycoprotein antigens specific for lung cancer were identified.

- 0854 A HUMAN LEUKEMIA CELL WITH BOTH B AND T CELL SURFACE RECEPTORS. (E.) Shevach, E. (Natl. Cancer Inst., Bethesda, Md.), R. Edelson, M. Frank, M. Lutzner and I. Green. *Proc Natl Acad Sci USA* 71(3):863-866, 1974.

The lymphocytes of a 64-year-old female with chronic lymphatic leukemia (CLL) were found to simultaneously

bear cell surface receptors of both B and T cells. Morphologically the cells from this patient were readily distinguishable from those in CLL and those in the Sezary syndrome. The percentage of peripheral blood lymphocytes binding sheep erythrocytes (E) was approximately 80% in this patient, while the percentage of cells binding antigen-antibody-complement complexes (EAC) was 35 to 49%. The mixed rosettes from a group of normal volunteers were predominantly composed of EAC with only one or two E cells, while the mixed rosettes observed in leukemic cells were generally composed of equal numbers of EAC and E. In contrast to normal human lymphocytes, about 20% of which bind aggregated IgG, less than 2% of the cells from this patient bound this reagent. In addition, only about 1-2% of the leukemia cells from the patient showed the presence of surface immunoglobulin (SIg), while about 20% of normal human lymphocytes show SIg. Thus, the patient in question had neither classical CLL nor Sezary syndrome, but rather a previously undescribed disease entity.

- 0855 IMMUNOGENICITY OF EMBRYONIC ANTIGENS ASSOCIATED WITH CHEMICALLY INDUCED RAT TUMOURS. (E.) Baldwin, R. W. (Cancer Res. Campaign Labs., U. Nottingham, England), D. Graves and B. M. Vose. *Int J Cancer* 13(1):135-142, 1974.

Serum and lymph-node cells (LNC) were taken from Wistar rats immunized against 4-dimethylaminoazobenzene-induced hepatomas and 3-methylcholanthrene-induced sarcomas and their cytotoxicity against plated embryo cells assayed. Both tumor-immune rat sera and LNC were cytotoxic for cultured embryo cells, the susceptibility of the embryo cells to cytotoxic antibody being dependent upon the age of the embryo. The induction of developing embryomas following the s.c. injection of 12- to 16-day-old embryo cells into adult syngeneic rats was not generally effective in inducing resistance to subsequent challenge with rat hepatomas or sarcomas. In rats challenged with hepatoma cells after receiving three weekly injections of irradiated embryo cells, neither tumor incidence nor growth was significantly affected; similar results were obtained in rats challenged with sarcoma cells. LNC and peritoneal exudate cells taken from multiparous pregnant rats were tested for their capacity to adoptively transfer resistance to hepatoma cells. Tumor development was not reduced in rats injected with a mixture of these lymphoid cells and hepatoma cells. Thus, although immunogenic, the tumor-associated embryonic antigen does not function as a tumor rejection antigen.

- 0856 TUMOR SPECIFIC ANTIGENS IN HUMAN RENAL CELL CARCINOMA AND COLON CARCINOMA: THEIR DEMONSTRATION, COMPARISON AND IMPLICATIONS FOR TUMOR RADIOLOGY. (E.) Jander, H. P. (U. Minnesota, Minneapolis). *Diss Abstr Int* 34(11):5544-B - 5545-B, 1974.

Rabbits were immunized with saline and perchloric acid extracts of neoplastic renal and colonic tissue, bled, and the antiserum absorbed with the corresponding normal tissue, human serum, human erythrocytes

of all blood groups, and bacterial antigens. Using the Ouchterlony microimmunodiffusion method, the individual renal cell carcinoma extracts showed reactions of identity among each other. With two exceptions, none of the absorbed antihypernephroma antisera reacted with any of nine normal kidney antigens. There were two highly specific hypernephroma antigens, two highly specific colon carcinoma antigens, and several bispecific antigens. Treatment with 1.0 M perchloric acid usually eliminated the antigenic activity of the renal cell carcinoma extracts but not the colon carcinoma antigens. Similarly, while the colon carcinoma antigens migrated in the beta region during immunoelectrophoresis, all but one of the renal cell carcinoma antigens had an alpha mobility. Heat stability at 80 C for 10 minutes was associated with beta mobility only. Evaluation of the data obtained in the analytical ultracentrifuge by Revets formula for spherical polymers indicated that the multiple peaks obtained from several individual antigen extracts were due to a process of random physical and chemical forces rather than polymerization of a basic antigenic unit.

0857 TUMOR-ASSOCIATED ANTIBODIES TO OCULAR AND CUTANEOUS MALIGNANT MELANOMAS: NEGATIVE INTERACTION WITH NORMAL CHOROIDAL MELANOCYTES. (E.) Federman, J. L. (Wills Eye Hosp., Philadelphia, Pa.), M. G. Lewis and W. H. Clark. *J Natl Cancer Inst* 52(2):587-589, 1974.

Tumor-associated humoral antibodies in the serum of patients with ocular melanomas and those with cutaneous melanomas were studied by indirect cytoplasmic immunofluorescence. Positive autologous reactions were observed in the four patients with primary ocular choroidal melanomas and in two patients with primary cutaneous melanomas. Allogeneic reactions were noted among the ocular patients, among the cutaneous patients, and between the two groups. Metastatic ocular melanoma cells showed allogeneic immunofluorescence with the serum from the four ocular patients and from one of the three cutaneous patients. The tumor-associated antibodies from both groups failed to react with allogeneic normal choroidal melanocytes. The normal choroidal melanocytes failed to show autologous reactivity. Normal serum and serum from a patient with mucoepidermoid carcinoma failed to react with the melanoma cells.

0858 CELL-MEDIATED IMMUNITY AND SPECIFIC SERUM FACTORS IN HUMAN CANCER: THE LEUKOCYTE ADHERENCE INHIBITION TEST. (E.) Maluish, A. (Dept. Microbiol., U. Queensland, Brisbane, Australia) and W. J. Halliday. *J Natl Cancer Inst* 52(5):1415-1420, 1974.

Blood leukocytes from patients with malignant melanoma (10 cases), adenocarcinoma of the colon and rectum (8 cases), and adenocarcinoma of the breast (1 case) reacted with aqueous extracts of tumors of the corresponding type, with the result that adherence of the leukocytes to glass was diminished. Leukocytes from normal individuals did not react, confirming that inhibitory activity with a tumor

patient's leukocytes was specific for tumor-associated antigen. The leukocyte adherence inhibition (LAI) test could be completed in a few hours. Sera from tumor-bearing patients blocked the LAI reaction of their own leukocytes or leukocytes from other patients with the same type of tumor. Serum blocking activity was lost soon after surgical removal of the tumor; the patient's serum then became unblocking. The LAI technique gave consistent results analogous to those reported with the lymphocyte toxicity test, and was easier and quicker.

0859 COMMON CELL SURFACE ANTIGEN ASSOCIATED WITH MAMMALIAN C-TYPE RNA VIRUSES: CELL MEMBRANE-BOUND gs ANTIGEN. (E.) Yoshiki, T. (New York Hosp.-Cornell U. Med. Coll., N.Y.), R. C. Mellors, W. D. Hardy, Jr. and E. Fleissner. *J Exp Med* 139(4):925-942, 1974.

An antibody which recognizes a common cell surface antigen associated with murine and feline C-type RNA viruses was previously demonstrated using rabbit anti-ether-disrupted feline leukemia virus (FeLV) antiserum and the indirect membrane immunofluorescence method. This common cell surface antigen was further studied using the indirect membrane immunofluorescence test and the absorption analysis of rabbit anti-FeLV, rabbit anti-FeLVp 30, and rabbit anti-murine leukemia virus p 30 (MuLVp 30). An antigen shared by murine and female C-type RNA leukemia and sarcoma viruses was detected on the surface of cells infected or transformed by C-type viruses. The antigen was characterized as membrane-bound gs antigen bearing two determinants: membrane-bound gs-1, intraspecies-specific antigenic determinant; and membrane-bound gs-3, interspecies-specific antigenic determinant. Membrane-bound gs antigen was located on the cell surface, frequently near the site of virus budding, but not on the envelope of murine C-type RNA virus.

0860 ANTIBODIES TO EPSTEIN-BARR VIRUS ASSOCIATED ANTIGENS IN RELATIVES OF CANCER PATIENTS. (E.) Levine, P. H. (Natl. Cancer Inst., Bethesda, Md.), J. F. Fraumeni, Jr., J. I. Reisher and D. W. Waggoner. *J Natl Cancer Inst* 52(4):1037-1040, 1974.

The possibility that Epstein-Barr virus (EBV) titers in lymphoma patients could be a result of the disease process or a marker of susceptibility to another oncogenic factor, rather than a specific response to a suspected etiologic agent (EBV), was investigated. Sera were collected from 21 families with multiple cases of cancer, including lymphomas, which permitted the prospective evaluation of normal individuals at high risk of developing tumors. Antibody levels to the EBV capsid antigen and early antigen were significantly higher in the 83 infected members of multiple-case families than in 144 normal controls. The differences between the cancer families and the controls were most prominent in individuals under the age of 20, since antibody to EBV-associated antigens appears higher in older individuals. Antibody titers were higher in families where the prominent

tumor types were carcinoma and soft-tissue sarcoma as well as lymphoma. High EBV titers in certain individuals, rather than reflecting a recent infection with EBV, may represent an abnormal immune response perhaps related to family susceptibility to cancer.

- 0861 ANTIGENIC CROSS-REACTIVITY BETWEEN BENIGN AND MALIGNANT NEOPLASMS OF THE HUMAN BREAST. (E.) Avis, F. (Sch. Med., U. North Carolina, Chapel Hill), I. Mosonov and G. Haughton. *J Natl Cancer Inst* 52(4):1041-1049, 1974.

Lymphocytes from 12 patients who had fibroadenoma alone or combined with fibrocystic disease of the breast were tested for their ability to kill related tumor target cells, normal fibroblasts, and cells of unrelated tumors. All patients had had their fibroadenoma excised and were without residual breast disease at the time of the study. Each showed specific cell-mediated immunity directed against breast adenocarcinoma cells, and there was no unexpected cross-reactivity with other types of tumor cells or with normal fibroblasts. Criss-cross type experiments confirmed the specificity of the antigenic cross-reactivity between patients with fibrocystic disease and breast adenocarcinoma cells. These results imply the existence of a common antigen on the cell surface of the fibroadenomas and adenocarcinomas of the breast.

- 0862 HL-A ANTIGENS IN HODGKIN'S DISEASE: HISTOPATHOLOGIC AND CLINICAL CORRELATIONS. (E.) Graff, K. S. (Natl. Cancer Inst., Bethesda, Md.), R. M. Simon, R. A. Yankee, V. T. DeVita and G. N. Rogentine. *J Natl Cancer Inst* 52(4):1087-1090, 1974.

HL-A antigens in 103 Hodgkin's disease patients were compared with those in 459 healthy controls. Only A5 was significantly more frequent in the total patient population, and this increase was related to the histologic type of Hodgkin's disease. A5 was increased in the mixed cellularity and lymphocyte-predominance histologic types. It was not elevated in patients with nodular sclerosis but seemed related to clinical stage of disease. A1, A8, and A18 were significantly increased in mixed-cellularity but not in the other histologic types. These findings suggest that the clinical and pathologic pattern of Hodgkin's disease is influenced by the HL-A phenotype of the host. Differences in the histologic subtypes in a patient population may account for variations in HL-A antigen in various studies.

- 0863 INHIBITION BY INTERFERON OF SV40 TUMOR ANTIGEN FORMATION IN CELLS INJECTED WITH SV40 cRNA TRANSCRIBED *IN VITRO*. (E.) Graessmann, A. (Inst. Moleculärbiochem., Freien U. Berlin, Germany), M. Graessmann, H. Hoffmann, J. Niebel, G. Brandner and N. Mueller. *FEBS Lett* 39(3):249-251, 1974.

Simian virus 40 (SV40) cRNA was synthesized *in vitro* with *E. coli* RNA polymerase and injected into monkey

kidney cells (TC7) by means of a microinjection technique. The SV40 cRNA-injected cells showed SV40 T-antigen within 24 hours. This SV40 cRNA-induced T-antigen formation was not inhibited by actinomycin D (1 µg/ml), or by treatment of the cRNA with pancreatic DNase. RNase and alkaline treatment destroyed the biological activity of the cRNA. The arrangement of T-antigen in the nuclei induced by *in vitro* cRNA was the same as in the SV40 virus infected cells. When TC7 cells were treated with human interferon (2000 units/ml) 18 hours prior to cRNA injection, only 0.1% of the cells were positive for SV40 T-antigen 24 hours after RNA injection compared to 40% of the control (non-interferon-treated) cells. The rate of reduction of T-antigen positive cells by interferon was in the same range when SV40 DNA was injected into the TC7 cells instead of virus cRNA. The data support the hypothesis that interferon inhibits primarily the translation of the SV40 genome.

- 0864 CULTURAL AND ANTIGENIC PROPERTIES OF NEWLY ESTABLISHED CELL STRAINS DERIVED FROM ADENOCARCINOMAS OF THE HUMAN COLON AND RECTUM. (E.) Tompkins, W. A. F. (Coll. Vet. Med., U. Illinois, Urbana), A. M. Watrach, J. D. Schmale, R. M. Schultz and J. A. Harris. *J Natl Cancer Inst* 52(4):1101-1110, 1974.

Two strains of neoplastic cells were established from adenocarcinomas of the human lower gastrointestinal tract. Both strains, human colon tumor-8 (HCT-8) and human rectal tumor-18 (HRT-18), grew as discrete and tightly packed colonies of epithelial cells, each with a large nucleus and scanty cytoplasm. Fairly uniform microvilli, disposed over the entire free surface of the cells, were frequently parallel, closely resembling the brush border of the intestinal epithelial cells. The strains were characterized by a short generation time and high plating efficiency. The cells formed colonies when plated on human fibroblasts but did not form colonies on fibroblasts from other species. Cytogenetic analysis of HCT-8 revealed a mode of 48 chromosomes at both low and high *in vitro* passage levels, with extra A and D chromosomes in approximately 90%. HRT-18 also had a mode of 48 chromosomes. However, the additional chromosomes were more random, appearing for the most part in groups D and F. Both HCT-8 and HRT-18 yielded high levels of carcinoembryonic antigen (CEA) *in vitro*, with most CEA in the culture supernatant and not cell associated.

- 0865 HUMAN LEUKEMIA CELL ANTIGENS: SEROLOGIC CHARACTERIZATION WITH XENOANTISERA. (E.) Mohanakumar, T. (Duke U. Med. Ctr., Durham, N.C.), R. S. Metzgar and D. S. Miller. *J Natl Cancer Inst* 52(5):1435-1444, 1974.

Antisera to different morphologic classes of human leukemia cells, produced in monkeys and chimpanzees, were, after appropriate absorptions, cytotoxic to leukocytes from patients with leukemia and some myeloproliferative disorders but not to leukocytes from normal donors or patients with other neoplastic and nonneoplastic diseases. Direct cytotoxicity

testing and absorption studies demonstrated that nonhuman primate antisera to cells from two different donors with chronic lymphocytic leukemia probably detected an antigen common to all acute and chronic lymphocyte leukemia patients. The non-human primate antisera to myeloid leukemia cells, however, detected more than one leukemia-associated antigen. Absorption studies on the nonhuman primate antisera to myeloid leukemia cells indicated an antigen specific for certain acute myelogenous leukemia cells and another antigen specific for certain chronic granulocytic leukemia cells. Another antigen(s) was cross reactive between cells from these two types of myeloid leukemia. Antisera to subcellular antigen components from human leukemia cells, produced in rabbits, were, after absorption, cytotoxic to cells from leukemia patients but not to leukocytes from normal donors. The rabbit antisera, however, did not distinguish between the morphologic classes of leukemia. Nonhuman primate antisera to monkey or myelogenous leukemia cells and a tissue culture cell line derived from a monkey myelogenous leukemia also detected neoantigens present on some human leukemic cells. The spectrum of antigens present on the surface of leukemic cells may all be considered leukemia-associated antigens.

0866 PARTIAL ISOLATION AND CHARACTERIZATION OF ANTIGEN(S) ASSOCIATED WITH MURINE MELANOMA. (E.) Bystryn, J. C. (New York U. Sch. Med., N.Y.), I. Schenkein, S. Baur and J. W. Uhr. *J Natl Cancer Inst* 52(4):1263-1269, 1974.

Antigens associated with murine B16 melanoma (MAA) were radiolabeled by the incubation of tumor cells with ^3H -leucine and identified by an antigen-binding radioimmunoassay. The MAA had a molecular wt of 150,000-200,000 daltons, were precipitable by 52% ammonium sulfate, and were inactivated by treatment with heat, acid, base, trypsin, or papain. Treatment with neuramidase greatly increased MAA antigenicity. These results suggest that MAA are glycoproteins. Some MAA were present to a lesser and variable extent in normal syngeneic murine (C57BL/6J) fibroblasts. MAA were released into culture medium by tumor cells and to a lesser extent by normal cells. It is suggested that antigen release could account for the greater frequency of immune response to normal antigens in patients with cancer and could provide a mechanism for escape from immune surveillance.

0867 HUMAN LEUKEMIA-ASSOCIATED ANTI-NUCLEAR REACTIVITY. (E.) Klein, G. (Karolinska Inst., Stockholm, Sweden), M. Steiner, F. Wiener and E. Klein. *Proc Natl Acad Sci USA* 71(3):685-689, 1974.

A brilliant, coarsely granular nuclear antigen was detected by anti-complement immunofluorescence in the nuclei of acute myeloid leukemia myeloblasts. Designated as LANA (leukemia-associated nuclear antigen), the reactivity differs from that of the Epstein-Barr-virus-determined nuclear antigen in immunological specificity and morphological appearance, although it is visualized by the same method.

Serum from acute myeloid leukemia patients gave positive reactions in 73% of the cases. In acute lymphatic leukemia, chronic myeloid leukemia, chronic lymphatic leukemia, and Burkitt's lymphoma the sera were positive in 35, 14, 19, and 24%, resp. Of 5 polyethemic sera, 2 were positive as were 2 of 11 myeloma sera. Among 61 healthy controls, 58 were negative, whereas 3 showed a diffuse nuclear staining with a different pattern. Sera from 20 patients who had recovered from infectious mononucleosis were all negative. In addition to the blasts of acute myeloid leukemia, a similar reactivity was seen with 2 Epstein-Barr virus DNA and Epstein-Barr-virus-determined nuclear antigen-negative African lymphoma biopsies and in a short-lived tissue culture line derived from one of them. LANA could be a fetal or tissue-specific antigen, a virally determined antigen, or a specific form of anti-nuclear reactivity.

0868 CELLULAR IMMUNITY IN MICE WITH SIMIAN VIRUS 40-INDUCED MKSA TUMORS: COMPARISON OF THREE ASSAYS OF TUMORIMMUNITY. (E.) Howell, S. B. (Natl. Cancer Inst., Bethesda, Md.), C. E. Esber and L. W. Law. *J Natl Cancer Inst* 54(4):1361-1363, 1974.

BALB/c mice with syngeneic simian virus-40-derived ascites tumors for 0-4 wk were tested for their cellular immune capacity by a combination of *in vivo* and *in vitro* assays. Early tumor growth was associated with detectable cellular immunity, as measured by direct tumor challenge with 10^6 cells s.c., the Winn test, and a modified microcytotoxicity assay. Animals with advanced tumors lost immunity detected by direct tumor challenge and the Winn test, whereas specific immunity detected by the microcytotoxicity assay persisted. These studies support previous concepts that the immune status of tumor-bearing mice is altered with increasing total tumor load. Additionally, the discrepancy between these assays performed in parallel may reflect functionally different components of the immune response to tumor-associated transplantation antigens.

0869 SEPARATION OF TWO DIFFERENT TUMORAL ANTIGENIC SPECIFICITIES AS TWO ISOANTIGENIC VARIANTS OBTAINED FROM A TUMOR INDUCED CHEMICALLY IN F_1 HYBRIDS (A. CA x A. BY). (Fr.) Oth, D. (I.N.S.E.R.M., Marseille, France) and Y. Barra. *C R Acad Sci [D] (Paris)* 278(1):177-180, 1974.

The relationship between tumor-associated transplantation antigens (TATA) and antigens dependent on the H2 histocompatibility system was investigated with the use of two isoantigenic variants of a tumor FAY_2 , which had been induced in a female F_1 hybrid mouse (A.CA x A.BY) by methylcholanthrene (0.1 mg s.c.). After two transplantations in hybrid mice, the FAY_2 tumor was transplanted into immunodepressed A.CA and A.BY mice. Successive passages (7-9) in the A.CA and A.BY mice, resp., produced tumor variants, A and Y, which were specific for the lines of mice in which they had been passed. The variants were then tested for their TATA specificity in F_1 (A.CA x A.BY) mice. The F_1

mice were first immunized by s.c. injection of irradiated tumor fragments 30 and 15 days before s.c. injection of viable tumor. Since no evidence of crossed immunity was observed, it is concluded that the two isoantigenic variants of the FAY2 tumor have different TATA specificities.

0870 MURINE AUTOANTIBODIES TO A CRYPTIC MEMBRANE ANTIGEN: POSSIBLE EXPLANATION FOR NEURAMINIDASE-INDUCED INCREASE IN CELL IMMUNOGENICITY. (E.) Rosenberg, S. A. (Harvard Med. Sch., Boston, Mass.) and S. Schwarz. *J Natl Cancer Inst* 52(4):1151-1155, 1974.

Normal sera of several mouse strains contained cytotoxic activity toward lymphocytes (10^7 - 10^8 cells) treated with neuraminidase (300 U) but not to untreated cells. The greatest cytotoxic activity was in C3H/HeJ mice. CBA/J and AKR/J mice also had high levels. In C57BL/6J mice there was no cytotoxic activity toward neuraminidase-treated lymphocytes. This cytotoxic activity (probably antibody) was complement dependent and stable at 56 C for 30 min, but was inactivated by heating to 80 C for 30 min. Neuraminidase-treated C3H/HeJ and C57BL/6J cells contained equal amounts of this "hidden" antigen, as determined by absorption studies. Untreated cells contained no detectable antigen. It is hypothesized that these natural antibodies to a "cryptic" antigen exposed by neuraminidase treatment alter a cell's immunologic processing, leading to an increased immunologic response to bystander tumor antigens capable of affecting the growth and viability of other cells containing these tumor antigens.

0871 LOW DOSE TOLERANCE PREVENTING TUMOR IMMUNITY. (E.) Kölsch, E. (Heinrich-Pette-Inst. Virol. Imm. Hamburg, Germany), R. Mengersen and E. Diller. *Eur J Cancer* 9(11/12):879-882, 1973.

Balb/c mice were inoculated three times at weekly intervals with various amounts of lethally irradiated Balb/c mastocytoma cells, after which the animals were challenged with 10^5 living mastocytoma cells. Significant immunity was conferred by 10^4 to 10^7 irradiated tumor cells, while animals pretreated with subimmunogenic doses of antigen had a significantly higher incidence of tumors than the animals receiving 1 or 10 irradiated cells. In a second experiment, animals pretreated for 7 weeks with 10^1 - 10^3 irradiated tumor cells challenged with 3×10^4 liver tumor cells developed tumors; similarly challenged non-pretreated controls developed no tumors. No cytotoxic or enhancing antibodies were demonstrated. In a third experiment, tumor frequency in untreated animals gradually decreased from 100% following the injection of 6×10^6 living mastocytoma cells to a plateau of 20% following the injection of 10^4 - 10^3 cells. When fewer than 10^3 cells were injected, the frequency of tumors increased. Thus, antigen in concentrations too low to immunize the host against tumor development is able to induce a status which facilitates the growth of tumor cells; this process differs from enhancement by antibodies. Thus, immunological intervention in cancer may be primarily

a problem of preventing or breaking low dose immunological tolerance.

0872 RECOVERY OF IMMUNE SYSTEM AFTER CIGARETTE SMOKING. (E.) Thomas, W. R. (Dept. Microbiol., U. Western Australia, Perth Med. Ctr., Shenton Park). P. G. Holt and D. Keast. *Nature* 248(5446):358-359, 1974.

Groups of mice were exposed to fresh cigarette smoke in a Hamburg II small animal smoking machine on week days. The animals were inoculated intratracheally with 10^8 sheep erythrocytes and 7 days later the direct and indirect plaque-forming cells (PFC) in the spleen, lungs, and mediastinal and cervical lymph nodes were determined. About 10^8 , 10^7 , and 10^6 leukocytes (predominantly lymphocytes) per cell preparation were obtained from the spleen, lymph nodes, and lung, respectively. There was no difference between the number of leukocytes in the cell preparations from normal mice and mice exposed to the smoke. The primary immune response in all organs was markedly depressed after 42 weeks of smoke exposure. Sixteen weeks after the cessation of smoking, the mice exhibited significantly increased direct PFC responses in the lungs and the lymph nodes draining the respiratory system. Although the average response in the spleen indicated recovery, the results were extremely variable. The indirect PFC responses also showed a depression after 42 weeks' smoke exposure in all organs, and a recovery 16 weeks after the cessation of smoke exposure. The phenomenon of "recovery" in human ex-smokers may be attributable, in part, to a similar restoration of immune function.

0873 IMMUNOLOGIC TOLERANCE TO ANTIGENS ASSOCIATED WITH MURINE LEUKEMIA VIRUSES: T-CELL UNRESPONSIVENESS? (E.) Chieco-Bianchi, L. (Natl. Cancer Inst., Bethesda, Md.), F. Sendo, T. Aoki and O. L. Barrera. *J Natl Cancer Inst* 52(4):1345-1350, 1974.

To test whether the cell-mediated immune response of murine leukemia virus (MuLV) carrier mice is specifically depressed, adult C57BL/6 mice, neonatally infected with Moloney (M)-MuLV, were immunized with M-MuLV-induced leukemia BALB/c cells (YC8, LSTRA). Their spleen lymphocytes were assayed at various intervals after immunization with syngeneic M-MuLV-induced leukemia cells (MBL-2) by use of ^{51}Cr -releasing lymphocyte-mediated cytotoxicity (LMC). In contrast with similarly immunized control mice, spleen lymphocytes from M-MuLV neonatally infected mice showed no reactivity, but these cells were fully reactive when tested against radiation-induced leukemia BALB/c cells (BALB.RL σ 1). No blocking activity to M-MuLV-associated antigens was found with different sera from M-MuLV neonatally infected and immunized mice. These results, together with the finding that the active lymphocytes in LMC were sensitive to pretreatment with anti- θ serum, suggest that a state of thymus-derived (T)-cell unresponsiveness occurs in neonatally infected mice. Though the neutralizing antibody to M-MuLV was not found in M-MuLV neonatally infected C57BL/6 mice,

another study showed the presence of specific humoral antibody to M-MuLV reverse transcriptase in the kidney eluate of similarly treated C57BL/6 mice. Therefore, partial tolerance to M-MuLV-associated antigens occurred in this system.

0874 BLOCKING EFFECT OF THE MIGRATION-INHIBITION REACTION BY SERA FROM IMMUNIZED SYNGENEIC MICE AND BY SERA FROM PLASMACYTOMA-BEARING BALB/c MICE. DETECTION OF FREE, CIRCULATING TUMOR ANTIGEN. (E.) Poupon, M.-F. (Inst. Sci. Res. Cancer, Villejuif, France), G. Lespinats and J.-P. Kolb. *J Natl Cancer Inst* 52(4):1127-1134, 1974.

A crude extract of BALB/c mouse plasmacytoma inhibited the migration of spleen cells from immunized BALB/c mice (2×10^5 live tumor cells, s.c. and i.p. alternately, twice weekly for three weeks). The dose necessary for significant inhibition was in the range 0.5-5 mg/ml. Sera of tumor-bearing mice, even at a dilution of 1/100, and sera of immunized syngeneic mice blocked this inhibition. A mixture of the two types of sera had either a blocking effect or no effect on the migration inhibition, depending on the relative concentrations. Furthermore, sera from tumor-bearing animals directly provoked a migration inhibition of immune spleen cells without the addition of extraneous antigen. These results indicated that sera of plasmacytoma bearers contained free, circulating tumor-specific antigen.

0875 NATURAL ANTIBODY IN HUMAN SERUM TO A NEO-ANTIGEN IN HUMAN CULTURED CELLS GROWN IN FETAL BOVINE SERUM. (E.) Irie, R. F. (Sch. Med., U. California, Los Angeles), K. Irie and D. L. Morton. *J Natl Cancer Inst* 52(4):1051-1058, 1974.

Human cells in tissue culture were found to acquire a new membrane antigen detectable by a natural antibody in human serum. Subsequent immune adherence experiments showed that the antigen originated from fetal calf serum used in the tissue culture medium, and that it was not γ -globulin in the bovine serum. Cultured cells from sarcomas, embryos, and melanomas contained higher concentrations of the antigen than those from carcinomas and normal tissue. Human sera from both cancer patients and normal donors contain natural antibody to this antigen. Therefore, this antigen may introduce artifacts in tumor immunology studies in which human sera are tested for serologic reactions against human cells cultured in bovine sera.

0876 β_2 -MICROGLOBULIN: OCCURRENCE IN FETAL LIFE AND MALIGNANCY. (E.) Kithier, K. (Michigan Cancer Fdn., Detroit), J. Cejka, J. Belamaric, M. Al-Sarraf, W. D. Peterson, Jr., V. K. Vaitkevicius and M. D. Poulik. *Clin Chim Acta* 52(3):293-299, 1974.

The occurrence and concentration of β_2 -microglobulin was studied in human fetal sera and other fetal fluids, the sera of pregnant women, cord blood sera, and the sera of patients with neoplastic and other

diseases. The levels of this protein were elevated in the fetal and cord sera compared to the levels in maternal and normal adult sera. The serum concentrations of β_2 -microglobulin paralleled the changes in concentration of the fetoprotein-specific proteins over the course of intrauterine development. The protein was also found in fetal urine, bile, meconium extracts, and amniotic fluids, and it was synthesized by fetal testis, liver, thymus, and kidney cells. Elevated levels of β_2 -microglobulin were observed in a significant percentage (45%) of patients with advanced malignant diseases, the highest levels being found in patients with myeloma malignancies. Hodgkin's disease patients did not have elevated levels of β_2 -microglobulin. Several samples of ascitic and pleural fluids from various cancer patients were also found to contain β_2 -microglobulin.

0877 SURFACE IMMUNOGLOBULINS OF LYMPHOCYTES IN CHRONIC LYMPHOCYTIC LEUKEMIA AND DISSEMINATED LYMPHOSARCOMA. (E.) Silberman, S. (Lab. Serv., VA Hosp., Hines, Ill.) and R. Schrek. *Exp Mol Pathol* 20(1):33-39, 1974.

Immunofluorescent staining was used to study the incidence of heavy and light chain determinants on the surface of blood lymphocytes from nine normal humans, 14 patients with chronic lymphocytic leukemia (CLL), seven patients with lymphosarcoma cell leukemia (LSL), and one patient with hairy cell leukemia. In CLL, the percentage (46%) of cells stained with fluorescein-labeled anti- μ antisera was greater than normal for all patients except one; the percentage of lymphocytes positive for γ and α chains did not vary significantly from normal. In LSL, there was a relative (compared with CLL) increase in cells stained with antisera to γ and μ heavy chains. The concomitant distribution of both heavy chain molecules in the same lymphocyte was further demonstrated by double fluorescent staining. A significant positive correlation was found between the percentage of lymphocytes positive for γ chain and the lymphocyte count in LSL patients. These results support the hypothesis that CLL and LSL are distinct lymphoproliferative disorders and that they arise from two different types of lymphocytes.

0878 ANTIBODY TO EPSTEIN-BARR VIRUS ANTIGENS: DETECTION IN INFECTIOUS MONONUCLEOSIS BY RADIO-IODINE LABELING. (E.) Shen, M.-H. (Bowling Green St. U., Ohio). *Diss Abstr Int* 34(11):5582-B, 1974.

A paired radio-iodine-labeled antibody technique (PRILAT) was used to detect antibody to Epstein-Barr (EB) virus-capsid antigen in patients with infectious mononucleosis (IM). Gamma-globulin from IM serum was labeled with ^{125}I and mixed with ^{131}I -labeled globulin from normal serum. The mixture was incubated with antigen-containing cells and normal cells. The amount of normal globulin adhering to the cell was used to estimate that portion of the immune serum protein which was nonspecific. Viral capsid antigen was detected by PRILAT in several established lymphoblastoid culture lines

derived from IM patients. The results were comparable to those obtained with the indirect immunofluorescence (IF) test. No EB virus antigen was found in fresh leukocytes from IM patients. The indirect single labeled radio-iodine antibody technique (ISLRAT) was used to detect antibodies against EB-virus-induced membrane antigen in the serum of IM patients. The technique is specific and twice as sensitive as the IF technique.

- 0879 PROCEDURE FOR ACTIVATING EPSTEIN-BARR VIRUS EARLY ANTIGEN IN NONPRODUCER CELLS BY 5-IODODEOXYURIDINE. (E.) Long, C. (Flow Labs., Inc., Rockville, Md.), J. G. Derge and B. Hampar. *J Natl Cancer Inst* 52(4):1355-1357, 1974.

A procedure is described for the activation of Epstein-Barr (EB) virus in nonproducer human lymphoblastoid cells by 5-iododeoxyuridine (IUDR). Exponentially growing cell cultures were exposed to IUDR for 24 hours, a period which proved sufficient to insure that a maximum number of cells could traverse the cell cycle to reach the critical S-1 period for activation. The optimal dose of IUDR for virus activation was 20 µg/ml. To enhance the efficiency of IUDR uptake by DNA, endogenous thymidine monophosphate synthesis was inhibited with modified HAT (hypoxanthine-aminopterin-thymidine) medium, in which the thymidine was replaced by IUDR. The method was tested using nonproducer Raji and NC-37 cells and producer EB-3 cells. Significant levels of early antigen-positive cells were obtained in the absence of viral structural antigen synthesis. The technique should be useful in routine seroepidemiologic studies. The procedure may have to be modified, however, depending on the particular cells and culture conditions employed.

- 0880 IMMUNOSUPPRESSION IN CHICKENS BY AFLATOXIN. (E.) Thaxton, J. P. (Dept. Poultry Sci., North Carolina St. U., Raleigh), H. T. Tung and P. B. Hamilton. *Poultry Sci* 53(2):721-725, 1974.

Aflatoxicosis was induced in male broiler chicks by incorporating aflatoxin (0, 0.625, 1.25, 2.5, 5.0, and 10 µg/g) in the diet from hatching. At 24 days of age, the birds were immunized with sheep red blood cells (SRBC). All concentrations of aflatoxin significantly depressed the formation of hemagglutinin (HA) 3, 6, and 9 days after SRBC injection, the degree of immunosuppression being directly related to the dietary aflatoxin concentration on days 3 and 6. In the birds fed the lower aflatoxin concentrations, the antibody levels reached a maximum 6 days after SRBC injection, decreasing thereafter. In the birds fed the 5 and 10 µg levels, the antibody levels did not reach their maxima until 12 days after SRBC injection. Initiating the feeding of aflatoxin at the same time that the antigen was injected gave similar though more variable results. The relative sizes of the bursa of Fabricius and the thymus were reduced by dietary aflatoxin. The stage of immunosuppression can account for the carcinogenicity of aflatoxin as well as the enhanced

susceptibility to some infectious agents found during aflatoxicosis.

- 0881 INFLUENCE OF IMMUNOLOGIC COMPETENCE OF THE HOST ON METASTASES INDUCED BY THE 3LL LEWIS TUMOR IN MICE. (E.) Carnaud, C. (Weizmann Inst. Sci., Rehovot, Israel), B. Hoch and N. Trainin. *J Natl Cancer Inst* 52(2):395-399, 1974.

The importance of host immunologic competence in the spontaneous metastasis of the 3LL Lewis lung carcinoma was investigated. Immunologic impairment was induced in C57BL/6 and C3HeB mice by sublethal irradiation (450 or 550 R), adult thymectomy plus irradiation, or neonatal thymectomy, and the mice were later challenged with 5×10^5 3LL tumor cells s.c. The number of lung metastases was significantly increased in these immunologically impaired animals, as compared with intact controls. Furthermore, immunologic restoration of these mice by injection of lymphoid cells (10^7 syngeneic spleen cells i.v.) or by thymus reimplantation reduced significantly the number of metastases when compared with the number of nonrestored mice. Immunologic impairment had a more striking effect on metastasis than on primary tumor growth; this suggested that the immunologic response of the host was more efficient with disseminated tumor foci than with a single tumor mass.

- 0882 RIBOSOMAL RNA SYNTHESIS IN WI-38 CELLS STIMULATED TO PROLIFERATE. (E.) Zardi, L. (Temple U. Sch. Med., Philadelphia, Pa.) and R. Baserga. *Exp Mol Pathol* 20(1):69-77, 1974.

When confluent monolayers of WI-38 human diploid fibroblasts were stimulated to proliferate by a change of medium containing 10% fresh serum, the synthesis of DNA began to increase within 12 to 15 hours. The uptake of ^3H -uridine and its incorporation into total cellular RNA began to increase within 1 hour and reached a maximum within 8 to 12 hours. The synthesis of ribosomal RNA increased within 2 hours and peaked within 8 hours. Only those nutritional changes which caused stimulation of cell proliferation also caused an increase in the synthesis of ribosomal RNA 8 hours after stimulation. Low concentrations of actinomycin D (0.08 µg/ml) effectively inhibited both ribosomal RNA synthesis and the entrance of the cells into the S phase. Thus, an increase in the synthesis of ribosomal RNA is a prerequisite for the entrance of the cells into the S phase.

- 0883 INTERACTION OF BLOOD-GROUP MN-LIKE CANCER ANTIGEN AND HUMAN CYTOTOXIN. (E.) Springer, G. F. (Evanston Hosp., Ill.) and P. R. Desai. *Naturwissenschaften* 61(1):38-39, 1974.

The immunodominant structure of the N antigen of the MN human blood-group system is branched and 1 branch terminates in a non-reducing beta-D-galactopyranosyl grouping while the other has a non-reducing terminal alpha-NANA linked to beta-D-galactopyranosyl. The M substance differs from the N substance

only in that alpha-NANA covers the terminal beta-D-galactopyranosyl of the human N specific grouping. A glycoprotein antigen closely related to those of the human blood-group MN system was found in the cell surface of the TA3-Ha subline of the ascites form of a mouse mammary adenocarcinoma. Both this non-primate antigen and the human blood-group N antigen possess extremely high and specific *Vicia* agglutinin inhibitory activity and both have galactopyranosyl and NANA as termini. The TA3-Ha mouse cancer which carries this blood-group N-like antigen on its surface is closely akin to human adenocarcinomas. The TA3 cancer has been transferred in mice through many generations and 2 sublines have occurred. The serological specificity of the *Vicia* agglutinin is closely related to the anti-T antigen which occurs in the sera of all adult humans and most animals. In investigating the effect of heat-inactivated human sera in the presence of complement on the Ha and St carcinoma the TA3-St cells were killed, while the TA3-Ha cells were completely resistant. However, after removal of the terminal NANA by sialidase, the latter became fully susceptible. Concomitant treatment with beta-galactosidase abolished the killing activity of human and other mammalian sera. This clearly indicates that the human cytotoxic serum factor is directed towards a beta-D-galactopyranosyl structure.

0884 COMBINED EFFECTS OF PHYTOHEMAGGLUTININ AND STAPHYLOCOCCAL ENTEROTOXIN B ON DEOXYRIBONUCLEIC ACID SYNTHESIS DURING BLAST TRANSFORMATION IN HUMAN LYMPHOCYTES. (E.) Shambaugh, G. E., III (Northwestern U. Med. Sch., Chicago, Ill.) and G. R. Blumenschein. *Infect Immun* 9(2):384-390, 1974.

Three mitogenic agents, phytohemagglutinin (PHA), staphylococcal enterotoxin B (SEB), and concanavalin A (Con A), were tested for their effects on DNA synthesis in normal human leukocytes. In the presence of optimal concentrations of PHA and SEB, tritiated thymidine incorporation was enhanced significantly. In the presence of graded concentrations of one of these mitogens combined with fixed optimal concentrations of the other, this enhancement was additive. When PHA or SEB was combined with Con A, the resulting thymidine incorporation was slightly lower than for either mitogen alone. Since puromycin inhibited thymidine incorporation in the presence of PHA and SEB, the additive effect of these mitogens was due to increased enzyme synthesis. To define potential differences in the mechanisms of action underlying the additive effect of SEB and PHA, the relative contribution of the *de novo* and salvage pathways for pyrimidine biosynthesis was tested with cytidine, a specific salvage pathway inhibitor. Cytidine (10^{-3} M) inhibited synthesis through the salvage pathway, but did not significantly alter the induction of carbamyl phosphate synthetase II, the rate-limiting enzyme for the *de novo* pathway. The inhibition of DNA synthesis by millimolar concentrations of cytidine in lymphocytes incubated with PHA and/or SEB indicated that the pyrimidines involved in the enhancement of DNA synthesis were derived largely via the salvage pathway.

0885 CONCURRENT INFECTIOUS MONONUCLEOSIS AND ACUTE MYELOCYTIC LEUKEMIA. (E.)

Langenhuysen, M. M. A. C. (Div. Hematol., Dept. Med., U. Hosp., Groningen, The Netherlands). *Acta Haematol* 51(2):121-127, 1974.

A case of infectious mononucleosis in conjunction with acute myelocytic leukemia is presented. The patient, a 14-year-old girl, was diagnosed as having acute myelocytic leukemia and was treated with prednisone and i.v. vincristine. Partial remission followed and the patient was dismissed from the hospital in good general condition. Two months later, she was readmitted to the hospital with symptoms of infectious mononucleosis. She was again dismissed from the hospital in good general condition 2 months later and she remained in good condition for 4 more months. She died 14 months after initial admission to the hospital. The course of the leukemia in this patient seemed not to have been influenced by the concurrent infection, in contrast to reports of prolonged survival in other patients with acute lymphocytic leukemia complicated by infectious mononucleosis.

0886 PRESENCE AND POSSIBLE ROLE OF ANTI-IgG ANTIBODIES IN HUMAN MALIGNANCY. (E.)

Hartmann, D. (McGill U. Cancer Res. Unit, Montreal, Canada) and M. G. Lewis. *Lancet* (7870):1318-1320, 1974.

A passive hemagglutination technique was used to determine the anti-IgG antibody titers in the sera of patients with cutaneous melanoma, osteosarcoma, cancer of the colon, ocular melanoma, and adenocarcinoma of the bowel. Various malignancies were associated with high anti-IgG titers, patients whose metastatic disease had spread beyond the regional lymph nodes constituting the majority of those with positive titers. In patients with widespread disease of localized tumors, serum agglutinators could not be detected. In two patients, changes in both antitumor and anti-Fab (serum agglutinators) antibodies were monitored over a period of time. There was an inverse relationship between these two antibody patterns. It is possible that some serum agglutinators are directed against exposed determinants on antitumor antibodies of the class IgG.

0887 HISTOPATHOLOGY OF IMMUNOLOGIC REGRESSION OF TUMOR METASTASIS IN THE LYMPH NODES.

(E.) Kodama, T. (Hokkaido U. Sch. Med., Sapporo, Japan), E. Gotohda, N. Takeichi, N. Kuzumaki and H. Kobayashi. *J Natl Cancer Inst* 52(3):931-935, 1974.

KMT-17 rat tumor cells and KMT-17 cells artificially infected with Friend virus (FV-KMT-17) were injected s.c. into the right foot pads of normal and Friend-tolerant WKA/Mk rats. In the normal rats, the KMT-17 tumor grew progressively, while the FV-KMT-17 tumor grew initially and then regressed. Within an average of 15 days, all of the FV-KMT-17 tumors had regressed completely. Both the KMT-17 and FV-KMT-17 tumors grew progressively without regression in the

Friend-tolerant animals. The tumor cells metastasized to the regional popliteal, lumbar, and inguinal lymph nodes and formed massive metastatic foci in these nodes. The lymph node metastases also regressed spontaneously in the normal rats, but did not regress in the Friend-tolerant animals. Histopathologically, the infiltration and proliferation of lymphoid cells, reticulum cells, and fibrocytes were noted in the regressing metastatic lymph node tumors as well as in the regressing foot pad tumors. Lymph node reactions such as temporary disappearance of follicles, intensive sinus histiocytosis, marked increase of large mononuclear cells, and plasmocytosis were apparent when the tumor cells metastasized to the lymph nodes. The regression of the metastatic lymph node tumors and the primary foot pad tumors in the syngeneic rats was due to an immunologic reaction of the host.

0888 CELL SURFACE GLYCOLIPID AND GLYCOPROTEIN GLYCOSYLTRANSFERASES OF NORMAL AND TRANSFORMED CELLS. (E.) Patt, L. M. (Coll. Med., U. Arizona, Tucson) and W. J. Grimes. *J Biol Chem* 249(13):4157-4165, 1974.

Normal and transformed mouse fibroblasts catalyze the transfer of sialic acid, galactose, N-acetyl-galactosamine, N-acetylglucosamine, glucose, and mannose from nucleotide sugar donors to glycolipids and glycoproteins. The enzyme activity is associated with intact cells. Kinetic parameters and optimal ion concentrations were determined for the glycosyltransferase activities detected when whole normal and transformed mouse cells were incubated with nucleotide sugar. Homogenization of the cells either decreased or did not affect the activity and adding unlabeled sugars did not affect the incorporation. Trypsin caused a 50% inhibition of observable activity only when present in concentrations which also caused significant cell destruction. Swiss SV40 transformed cells showed decreased sialic acid-transferring ability compared with the parent cell line, and Swiss polyoma transformed cells showed reduced ability to catalyze the transfer of N-acetyl-galactosamine to glycolipids compared with the normal cell line. The *in vitro* whole cell reactions probably reflect the normal cellular systems which are synthesizing glycoproteins and glycolipids. Evidence supporting this conclusion was obtained from experiments in which glycolipid products synthesized in cells incubated in the presence of (^3H)galactose and UDP-(^{14}C) galactose were compared.

0889 LOCATION OF THE AVIAN TUMOR VIRUS GROUP SPECIFIC ANTIGEN IN THE BAI STRAIN A VIRUS ASSOCIATED MYELOBLAST CELL. (E.) Rao, P. R. (Dept. Zool., Osmania U., Post-Grad. Ctr., India). *Experientia* 30(5):540-541, 1974.

Nucleus membrane fractions and nuclei without membranes were prepared from myeloblasts collected from leukemic chickens. These fractions were obtained using two methods of disruption: breakage in a wig-L-Bug instrument, and homogenization with a glass pestle. There was a marked difference

in group specific (gs) antigen distribution between the fractions obtained by the two methods. In the wig-L-Bug fractions, most of the antigen was associated with the fraction containing the membranes, while in the pestle preparations, most of the antigen was found in the soluble fraction (obtained after sedimenting the microsomes from the microsome fraction). Variable and relatively small amounts of antigen were associated with the mitochondrial and microsome fractions. The nuclei preparations showed no trace of antigen. Thus, the antigen is primarily concentrated in the cell membrane, and it is likely that the BAI strain A virus is synthesized in association with the cell membrane of the infected cell.

0890 AUTOGENOUS IMMUNITY TO ENDOGENOUS RNA TUMOR VIRUS. IDENTIFICATION OF ANTIBODY REACTIVITY TO SELECT VIRAL ANTIGENS. (E.) Ihle, J. N. (Carcinogenesis Program, Biol. Div., Oak Ridge Natl. Lab., Tenn.), M. G. Hanna, Jr., L. E. Roberson and F. T. Kenney. *J Exp Med* 139(6):1568-1580, 1974.

The viral antigenic determinants recognized in an autogenous immune response in mice against their endogenous C-type virus were identified by SDS-polyacrylamide gel electrophoresis of immune precipitates between various sera and H^3 -labeled intact or disrupted AKR leukemia virus. Normal B6C3F₁ ((C57BL/6 X C3H/AnF)_F₁) serum reacts with viral envelope antigens having molecular weights of approximately 68,000, 43,000, and 17,000. In addition, minor reactions with viral antigens having molecular weights of approximately 19,000 and 15,000 are demonstrable. The 68,000 and 43,000 molecular weight antigens can be labeled with (^3H)glucosamine and may correspond to the major viral envelope antigens M₂ and M₁, respectively. The antigens recognized by autogenous immune sera do not differ with respect to the age of the animal, nor are they insignificantly different in sera from various strains of mice (BALB/c, C57BL/6, and C3H/AnF). These results suggest that the age-associated and strain variations in the autogenous immune response, as determined by radioimmune precipitation assays against intact virus, are due to quantitative and qualitative alterations of antibody levels against common antigens.

0891 RAT ALPHA₁ FETOPROTEIN. V. CATABOLISM AND FETAL-MATERNAL DISTRIBUTION. (E.) Sell, S. (Dept. Path., U. California, San Diego, La Jolla) and D. Alexander. *J Natl Cancer Inst* 52(5):1483-1489, 1974.

Normal adult, lactating adult, and pregnant Sprague-Dawley rats were injected with radiolabeled, highly purified alpha₁ fetoprotein ($\alpha_1\text{F}$) and the rates of catabolism and the distribution of the protein were determined by whole body and serum radioactivity counts; the serum $\alpha_1\text{F}$ concentrations were measured by radioimmunoassay. The concentration of $\alpha_1\text{F}$ at term was 5000 $\mu\text{g/ml}$ in the fetal serum, 1500 $\mu\text{g/ml}$ in the amniotic fluid, and 200 $\mu\text{g/ml}$ in the maternal

serum. There was an equilibration of α_1 F between the fetal blood, amniotic fluid, and maternal blood. The half-life of α_1 F in normal and lactating rats was 1 day, whereas it was 12-15 hours in pregnant animals. This was due to a catabolic site in the fetus or placenta that could be identified during the last week of gestation. This site was not specific for α_1 F since the catabolism of albumin was also more rapid in pregnant versus normal and lactating rats. Although α_1 F must perform the same osmotic function in the newborn as albumin does in the adult, its precise physiologic function remains unknown.

0892 IMMUNOLOGIC SIMILARITIES BETWEEN FETAL CELL ANTIGENS AND TUMOR CELL ANTIGENS IN GUINEA PIGS. (E.) Grant, J. P. (Nat'l. Cancer Inst., Bethesda, Md.), S. Ladich and S. A. Wells, Jr. *Cancer* 33(2):376-383, 1974.

Inbred strain 2/N guinea pigs were immunized with irradiated cells from two different methylcholanthrene-induced syngeneic guinea pig sarcomas (MCA-A and MCA-25), syngeneic second trimester fetal tissue, or allogeneic strain 13/N guinea pig tissue. In one experiment, immunized animals and multiparous strain 2/N females were injected intradermally with membrane antigen extracts (MEA) of each immunizing tissue and normal strain 2/N tissue, and subsequently evaluated from the development of delayed cutaneous hypersensitivity reactions (DCHR). Animals immunized to either tumor showed positive DCHR to MAE of that tumor and occasional reactions to MAE of the other tumor. Multiparous females and females immune to second trimester fetal tissue developed positive DCHR to fetal tissue MAE and to MAE of each tumor. In a second experiment, immunized animals and multiparous females were challenged s.c. with viable MCA-25 tumor cells. Significant resistance to tumor growth was demonstrated in animals immunized to either tumor, multiparous females, and animals immunized to second trimester fetal tissues. A similarity between fetal antigens and tumor-associated transplantation antigens of the two MCA-induced guinea pig sarcomas is suggested.

0893 DOUBLE-ANTIBODY RADIOIMMUNOASSAY FOR B16 MELANOMA ANTIBODIES. (E.) Bystry, J.-C. (New York U. Sch. Med.), I. Schenkein and J. W. Uhr. *J Nat'l Cancer Inst* 52(3):911-915, 1974.

Using a newly developed double-antibody radioimmunoassay, the development of antibodies to B16 melanoma-associated antigens (MAA) was measured during the natural growth of this tumor in C57BL/6J mice. The assay was based on the coprecipitation by anti-immunoglobulin of complexes of radiolabeled MAA with tumor antibodies. The MAA were radiolabeled by incubation of the melanoma cells in tissue culture with 3 H-leucine. Serum obtained from C57BL/6J mice immunized by repeated injections of irradiated B16 melanoma cells bound 4-8 times as much radiolabeled MAA as did the serum of normal control mice. The relationship was linear between the amount of MAA bound and the amount of antiserum used. The assay

was sufficiently sensitive and reproducible to measure changes in the levels of antibodies to B16 melanoma during its natural growth. The antibody levels declined during the late phase of tumor growth. There were cross-reactions between the sera of mice immunized against mammary adenocarcinomas and MAA and between antimeelanoma sera and antigens in syngeneic fibroblasts. This suggests the presence of shared antigenic determinants between these tumors and normal mouse tissue.

0894 SEROLOGIC ANALYSIS OF THE ANTIGENIC SPECIFICITIES OF SIMIAN VIRUS 40-TRANSFORMED CELLS AND THEIR RELATIONSHIP TO TUMOR-ASSOCIATED TRANSPLANTATION ANTIGEN. (E.) Ting, C.-C. (Nat'l. Cancer Inst., Bethesda, Md.), J. R. Ortaldo and R. B. Herberman. *J Nat'l Cancer Inst* 52(3):815-821, 1974.

In tests using the isotopic antiglobulin technique, the antisera produced by immunization of (BALB/c X C57BL)F₁ mice with syngeneic simian virus 40 (SV40) tumor (SVT2) reacted against at least two different specificities. Some sera only reacted with the tumor-associated cell-surface antigen (TASA) of the SV40-transformed cells. Other sera also reacted with a common antigen found in non-SV40 tumor cells but not in normal spleen cells. Only TASA was correlated with the tumor-associated transplantation antigen. Although all sera reacted with various SV40-transformed cells, they had different patterns of reactivity. Thus, SV40-transformed mouse cells possess both tumor-associated antigen, which is specific for SV40 tumor cells, and common antigen(s), which is shared by non-SV40 tumors and fetal tissue. Each of these antigens may consist of several molecular or several antigenic determinants and all of them may arouse humoral antibody responses differently.

0895 ANALYTICAL STUDY OF SALIVARY IMMUNOGLOBULINS IN MULTIPLE MYELOMA. (E.) Coelho, I. M. (Gulbenkian Inst. Sci., Pharmacol. Lab., Oeiras, Portugal), M. T. Pereira and G. Virella. *Clin Exp Immunol* 17(3):417-426, 1974.

Salivary immunoglobulins from ten patients with multiple myeloma were characterized immunochemically. Seven of the patients had IgA monoclonal components and their transfer to the saliva could be proved immunochemically in five patients. Three salivas containing monoclonal IgA were fractionated by gel filtration on Sephadex G-200, secretory component being detectable in the same peaks as the monoclonal IgA. Molecular size studies using electrophoresis in sodium dodecyl sulfate-polyacrylamide gel showed that, in most salivas oligomeric forms of IgA were exclusively or predominantly present. These findings suggest that oligomeric IgA of systemic origin might be as effectively transferred to external secretions as oligomeric IgA of regional origin. Of the three remaining patients, two had IgG monoclonal proteins which could be detected in the concentrated saliva, while the monoclonal component of the last

patient was of light chain type. In this last patient, no free light chains were detected in the concentrated saliva, but normal IgA and an apparently increased amount of polyclonal IgG were evident.

0896 IMMUNOFLUORESCENT STUDIES OF LYMPHOID TISSUE IN HODGKIN'S DISEASE. (E.)

Denton, P. M. (Inst. Cancer Res., Royal Marsden Hosp., Sutton, Surrey, England) and E. O. Field. *Tumors* 59:375-381, 1973.

Cell suspensions were prepared from fresh lymph nodes or spleens taken from 48 Hodgkin's disease patients. The cells were then incubated in sera from the same patients obtained during an active phase of their disease. An indirect immunofluorescent technique was used to detect the possible presence of antibodies in the serum directed against the spleen and/or lymph node cells. The indirect test failed to demonstrate the presence of autoantibodies in the sera tested. However, when samples of tissue were treated directly with fluorescein conjugate, positive cytoplasmic fluorescence appeared in a number of specific cell types in tissues affected by the disease. Most of the cells belonged to the plasma cell and transformed lymphocyte series and they also showed strong cytoplasmic affinity for pyronin. Quantitative and qualitative differences in the degree of fluorescence were observed in the sera of patients in different histological stages of Hodgkin's disease; positive cytoplasmic fluorescence was seen in more samples from the "mixed cellularity" and "lymphocyte depletion" groups than in samples from the "lymphocyte predominance" and "nodular sclerosis" groups. No evidence of cytoplasmic fluorescence was seen in 17 samples of tissue which was unaffected by disease. The antibody detected in the diseased tissue belonged mainly to the IgG class of immunoglobulin, although a few cells contained IgM.

0897 HUMAN THYMUS-LEUKEMIA RELATED ANTIGEN(S): DETECTION BY A NONHUMAN PRIMATE ANTISERUM.

(E.) Mohanakumar, T. (Duke U. Med. Ctr., Durham, N.C.) and R. S. Metzgar. *Cell Immunol* 12(1):30-36, 1974.

An antiserum against human thymus cells was produced in an adult *Macaca speciosa* monkey. The activity of the antiserum was then studied by cytotoxicity, mixed agglutination, and immune adherence techniques. The monkey antihuman thymus serum absorbed with human blood group AB erythrocyte (HRBC) reacted by cytotoxicity and immune adherence with human lymphocytes, skin fibroblasts, and thymocytes from a variety of donors. No antibody had been demonstrated in this serum which is specific for human peripheral T lymphocytes. The HRBC absorbed antiserum was additionally absorbed with peripheral blood leukocytes (HWBC) from normal blood donors; it failed to react with peripheral blood lymphocytes but still reacted strongly with thymocytes from a variety of adult and fetal donors, as well as with cells from acute (ALL) and chronic lymphocyte leu-

kemia (CLL) patients, cells from some acute myeloid leukemia (AML) and chronic granulocytic leukemia (CGL) patients, and two lymphoblastoid cell lines derived from normal donors. The antiserum absorbed with LCL failed to react with cells from ALL and CLL patients who were in the remission stage of their disease, and the monkey antiserum absorbed with cells from a CLL patient removed the reactivity for all leukemia donors. Absorption with thymocytes from each of three different donors removed the reactivity for cells from thymus donors, leukemic patients, and LCL. Thus, the monkey antiserum was detecting several different antigens other than those which are species-specific or HL-A related.

0898 ACTINOMYCIN D AND X-RADIATION SUPPRESSION OF SPONTANEOUS TUMORIGENESIS IN MICE. (E.)

Mason, J. M. (U. Tennessee Med. Units, Dept. Path., Memphis) and B. R. Jennings. *J Reticuloendothel Soc* 15(2):96-111, 1974.

The effects of immunosuppressive treatment on the rate of formation of spontaneous mammary neoplasms in Swiss mice was investigated. Six-to-eight-week-old virgin female Hale-Stoner Swiss mice were treated with lyophilized actinomycin D (4 µg) and/or 100 rad X-radiation. The two treatments combined delayed the appearance of mammary tumors 6 months and reduced their incidence by more than 1/2. The treatments also suppressed the synthesis of sheep hemagglutinins by more than 99% for at least 39 days. All of these effects were magnified when the animals were treated with 5, as opposed to 1, weekly doses of both agents. Four weekly doses of both agents, begun at 3.8 or 5.5 months of age, did not inhibit tumorigenesis. Treatment of recipients of primary mammary tumor isografts with actinomycin D and X-radiation reduced the growth rate of the transplanted tumors but did not influence the final incidence of successful transplants. When mice with palpable spontaneous mammary tumors were treated with five weekly doses of the immunosuppressants, tumor growth was inhibited by less than 40% compared with tumors on untreated mice. The rate of appearance of additional tumors in these mice was the same in both the treated and untreated groups. A lymphocytic accumulation was observed which appeared to be limited to the stroma of tumors excised from untreated mice. However, lymphocytes infiltrated the parenchyma of some tumors taken from mice receiving actinomycin D and radiation.

0899 SEPARABLE POPULATIONS OF ACTIVATED THYMUS-DERIVED LYMPHOCYTES IDENTIFIED IN TWO ASSAYS FOR CELL-MEDIATED IMMUNITY TO MURINE TUMOR ALLOGRAFTS. (E.)

Tigelaar, R. E. (Tumor Immunol. Unit. Imp. Cancer Res. Fund, U. Coll. London, England) and R. M. Gorczynski. *J Exp Med* 140(1):267-289, 1974.

The immune response of C57BL mice to DBA/2 tumor allografts was assessed using two assays of cell-mediated immunity: the *in vitro* lysis of ⁵¹Cr-labeled target cells, and the antigen-mediated inhibition of macrophage migration. Both assays

measured a T-cell-mediated reaction, and there was evidence that distinct subpopulations of T cells mediated these reactions. The tissue distributions of these activities was distinctive; both activities were present in the spleens from i.p. immunized mice, but only macrophage migration inhibition activity was present in the peripheral lymph nodes (PLN). Adoptive transfer of immune spleen cells into irradiated syngeneic recipients indicated that, while a substantial amount of migration inhibition activity could subsequently be found in the PLN, cytotoxic activity was found primarily in the spleens of the adoptive hosts. Velocity sedimentation analysis of the immune cells 14 days after i.p. immunization indicated that, while the majority of the cytotoxic activity was associated with small and medium lymphocytes, the majority of the migration inhibition activity was associated with medium and large lymphocytes. In addition, normal spleen cells were fractionated by velocity sedimentation immediately before allosensitization *in vitro*. Subsequent analysis of the sensitized fractions revealed that the activity profiles for cytotoxicity and macrophage migration inhibition were not coincident.

0900 ROSETTE-FORMING LYMPHOCYTES IN NORMALS AND PATIENTS WITH MALIGNANT LYMPHOMAS. (E.)

Cohnen, G. (Dept. Med., U. Essen, Germany), W. Augener, A. Buka and G. Brittinger. *Acta Haematol* 51(2):65-75, 1974.

The peripheral blood lymphocytes forming spontaneous rosettes with sheep red blood cells (RFL) were studied in normal individuals and patients with malignant lymphomas. Rosette formation was temperature dependent and was inhibited by treatment of the lymphocytes with sodium azide or trypsin, but not by preincubation with an anti-human immunoglobulin IgG preparation. In the normal individuals, 45-80% of the peripheral blood lymphocytes formed rosettes, while in the patients with chronic lymphocytic leukemia and in a patient with leukemic IgM-producing malignant lymphoma, the percentage of RFL was greatly reduced (3-9%). In patients with Hodgkin's disease, lymphocytic lymphosarcoma, reticulum-cell sarcoma, giant follicular lymphoma, Ig-producing lymphoma, and multiple myeloma, the proportion of RFL was either diminished or within the normal range (20-63%). Thus, the determination of blood lymphocytes with T or B cell characteristics does not contribute to the differentiation between the various forms of non-leukemic malignant lymphomas.

0901 SERUM NEUTRALIZING ANTIBODY DEVELOPMENT AND HOST RESISTANCE IN CHICKENS EXPOSED TO MAREK'S DISEASE INFECTION. (E.) Hong, C. C. (Paige Lab., U. Massachusetts, Amherst) and M. Sevoian. *Poultry Sci* 53(3):1110-1113, 1974.

The activity of serum neutralizing (SN) antibodies in both resistant and susceptible (to Marek's disease) line chickens was quantitated by SN tests against the JM strain of Marek's disease virus (MDV) *in vitro*. The resistant JM-N and K-line chickens

had significantly lower mortality rates from Marek's disease following MDV inoculation than the susceptible JM-P and S-lines. No significant difference in leukosis mortality was found between the resistant and susceptible strains when challenged with similar doses of JM virus. The SN antibody (maternal) titers in day-old chicks of all strains were low. Following inoculation with JM virus, the levels of SN antibody at 3, 6, 9, and 12 weeks were significantly higher in the resistant lines than in the susceptible lines. Thus, there appears to be a positive correlation between the ability to produce SN antibody and resistance to Marek's disease.

0902 EXPRESSION OF POLYOMA-INDUCED ANTIGENS IN LOW MALIGNANT HYBRIDS DERIVED FROM FUSION OF A POLYOMA-INDUCED TUMOUR WITH A FIBROBLAST LINE. (E.) Meyer, G. (INSERM, Marseille, France), M. Berebbi and G. Klein. *Nature* 249(5452):47-49, 1974.

Hybrid cells (A9/SEWA) derived from the fusion of cells of polyoma-induced sarcoma (SEWA) and an aneuploid fibroblast line of L origin (A9) were analyzed for the presence of the polyoma-specific surface antigen, karyotype, transplantability, and the presence of T antigen. The A9/SEWA and parental SEWA cells were positive for T antigen, while the parental A9 strain was negative. The hybrid line carried the polyoma-specific membrane antigen, as shown by immunofluorescence. Experiments with antiserum absorption showed no significant differences between the parental and hybrid lines. The presence of surface histocompatibility antigens, as measured by immunofluorescence, indicated that the viral genome was expressed in the hybrid cells. The data support the hypothesis that, although virally determined antigens may be necessary for the malignant behavior of the polyoma transformed cell, with the appropriate genetic or epigenetic constitution, other modifying factors may play a decisive role for the realization of the virally determined neoplastic potential.

0903 *IN VITRO* CLONING OF A RAT ASCITES HEPATOMA CELL LINE, AH66, WITH SPECIAL REFERENCE TO ALPHA-FETOPROTEIN SYNTHESIS. (E.) Tsukada, Y. (Hokkaido U. Sch. Med., Japan), M. Mikuni and H. Hirai. *Int J Cancer* 13:196-202, 1974.

Nineteen clones isolated from the AH66 ascites hepatoma cell line were investigated for alpha-fetoprotein (AFP) production *in vitro*. The original AH66 line synthesized 19 µg/ml of AFP in 7 days, while 15 of the clones synthesized 7-25 µg/ml AFP, and four clones synthesized extremely small amounts of AFP. The highest producing clone produced about 1000 times more AFP than the lowest producing clone. The clonal cells grew well after i.p. transplantation into Donryu rats. Most of the high-AFP producing clones resulted in shorter survival times following transplantation than the parental AH66 line; the survival times of the animals treated with the low producing times were comparatively longer. AFP production *in vivo* was comparable to that *in vitro*, while the amount of AFP produced by AH66 cells *in vitro* was about 12 times higher than *in vivo*. No

correlation was found between the modal chromosome number in the various clones and the AFP production. The results indicate that tumor cells exist as a mixed cell population and that selection or adaptation of this population takes place following changes in culture conditions.

0904 KINETICS OF THE ANTI-TUMOR DELAYED HYPERSENSITIVITY RESPONSE IN MICE WITH PROGRESSIVELY GROWING TUMORS: STIMULATION FOLLOWED BY SPECIFIC SUPPRESSION. (E.) Paranjpe, M. S. (Nat'l. Cancer Inst., Bethesda, Md.) and C. W. Boone. *Int J Cancer* 13(2):179-186, 1974.

At various times during the progressive growth of transplanted simian virus 40 (SV40)- and methylcholanthrene-induced fibrosarcomas in male BALB/c AnN mice, the delayed hypersensitivity (DH) response to tumor cells was determined using a quantitative radioisotopic foot-pad assay. For the first 7 days, a close correlation was found between tumor size and the degree of DH reactivity. After this time, as the tumor grew in size, the DH response declined to nondetectable levels. Following excision of the tumors, the DH response returned to a high level. This suppression, or "eclipse", of the antitumor cellular immune response in animals bearing tumors beyond a certain size (about 0.18 g) was specific for the types of tumor used. The spleen lymphocytes from unresponsive tumor-bearing mice still supported a positive DH reaction when mixed with tumor cells and injected into the foot-pads of normal mice. The results indicate that the transplanted tumor may elaborate soluble substances, especially antigenic substances, which travel through the blood stream and block the central immune response, possibly in association with blocking antibody. The eclipse phenomenon is important with regard to the treatment of cancer with vaccines derived from tumor tissues.

0905 ACCELERATED DEVELOPMENT OF TRANSPLANTED MAMMARY TUMORS IN MICE PRETREATED WITH THE METHANOL EXTRACTION RESIDUE OF BCG AND PREVENTION OF ACCELERATION BY CONCOMITANT SPECIFIC IMMUNIZATION. (E.) Jacobs, D. M. (Dept. Biol., U. California, San Diego, La Jolla) and M. L. Kripke. *J Nat'l Cancer Inst* 52(1):219-224, 1974.

Pretreatment of BALB/cfC3H mice with the methanol extraction residue (MER, two 0.5 mg injections i.p.) of *Bacillus Calmette Guérin* 14 and 3 days before challenge with syngeneic MTV+ mammary tumors (1 mm³ s.c.) resulted in an increased incidence of tumors compared with that in the saline-treated controls. When the animals were treated with MER several weeks before tumor challenge, tumor development was also accelerated. Faster tumor development did not seem related to the immunogenicity of these tumors, since acceleration was noted in syngeneic BALB/cfC3H (MTV+) mice in which these tumors were not detectably immunogenic, and also in syngeneic BALB/c (MTV-) hosts in which the tumors were strongly immunogenic. When MER treatment of either MTV+ or MTV- hosts was combined with specific tumor immunization, more rapid development

of the challenge tumors did not occur, but there appeared to be no added beneficial effect of the combined treatment over immunization alone.

0906 EPSTEIN-BARR VIRUS-NEGATIVE HUMAN MALIGNANT T-CELL LINES. (E.) Kaplan, J. (Child Res. Ctr. Michigan, Detroit), T. C. Shope and W. D. Peterson, Jr. *J Exp Med* 139(5):1070-1076, 1974.

Unlike the CCRF-SB, Raji, and P₃HR1 cell lines, the two malignant lymphoblastoid lines CCRF-CEM and HSB-2, which were derived from two children with leukemia secondary to lymphosarcoma, are T cells. They form rosettes with sheep erythrocytes and lack complement receptors and surface immunoglobulin. In addition, these cells bear many additional similarities to normal peripheral blood T cells. In contrast to rabbit antisera to the B-cell lines CCRF-SB and Raji, rabbit antisera to CCRF-CEM as well as equine antihuman thymocyte gamma globulin inhibit rosette formation with sheep erythrocytes by normal peripheral T cells as well as by both T-cell lines. Thus, the T-cell lines, but not the B-cell lines, share a common surface antigen with normal peripheral blood T cells. Unlike the B-cell lines, CCRF-CEM and HSB-2 lack Epstein-Barr virus antigens.

0907 DETECTION OF IMMUNE COMPLEXES USING ¹²⁵I GOAT ANTI(HUMAN IgG) MONOVALENT (Fab') ANTIBODY FRAGMENTS. (E.) Ludwig, F. J. (Coll. Med., U. Florida, Gainesville) and C. L. Cusumano. *J Nat'l Cancer Inst* 52(5):1529-1536, 1974.

Separation and identification of immune complexes in serum were based on sucrose gradient velocity sedimentation of samples labeled with radioactive monovalent antibody (Fab' fragments) to human immunoglobulin. *In vitro* complexes formed from tetanus toxoid and human antitoxoid (TATC) appeared in the gradient as a "radio-peak" sedimenting at 10S rather than the normal 7S position for human immunoglobulin G (HuIgG). These complexes were stable under the conditions of the gradient. They could be dissociated at low pH and separated by filtration into two fractions: one which sedimented at the 7S position of HuIgG when centrifuged with ¹²⁵I Fab, and another which reformed TATC after incubation with fresh tetanus-immune globulin and centrifugation with ¹²⁵I Fab. As little as 13 µg IgG could be detected easily by this technique; complexed IgG was quantified on the assumption that its interaction with ¹²⁵I Fab was similar to that of free IgG. A similar 10-11S radiopeak appeared in sera from five cancer patients and one patient with Weber-Christian disease. Similar peaks were not seen in sera from 10 normal healthy controls. A study of serial serum samples from a patient with cryptogenic adenocarcinoma with a single liver metastasis showed a 10-11S radiopeak in preoperation serum that was significantly reduced 1 week after removal of the tumor. In serum taken 1 month after surgery, a small peak reappeared; recurrent disease was found subsequently. This method may have potential for detecting and isolating tumor antigens and the corresponding antibody for diagnostic tests and basic immunologic studies.

0908 STABILIZATION OF ANTIGENS ON SURFACES OF MALIGNANT CELLS BY FORMALIN TREATMENT.

(E.) Kudo, T. (Nat'l. Cancer Inst., Bethesda, Md.), T. Aoki and J. L. Morrison. *J Nat'l Cancer Inst* 52(5): 1552-1557, 1974.

Chemical carcinogen-induced C57BL leukemia EL4 and Gross (G) virus-induced C57BL/6 leukemia E δ G2 were fixed with 0.1% formalin at 4 C for 7 days and tested for a) fixation effects and b) preservation of antigenic activity *in vitro* and *in vivo*. The formalin concentration was the optimal one in the pretested range of 0.1-10%. 1) Trypan blue exclusion in *in vitro* studies of fixation effects did not correspond with the results of *in vivo* tests; no incidence of tumor was observed in C57BL/6 mice inoculated i.p. with 10⁷ fixed EL4 and E δ G2 cells and in newborn C57BL/6 mice inoculated with 5 X 10⁶ fixed E δ G2 cells, though many fixed cells excluded trypan blue. 2) In *in vitro* tests, the amount of H-2^b antigen on fixed EL4 and E δ G2 cells, measured by absorption tests, was well preserved up to 28 days fixation; G surface antigens on fixed E δ G2 cells were preserved up to 7 days. When formalin-treated EL4 or E δ G2 cells were used for immunization in allogeneic or syngeneic systems, anti-serum from immunized mice reacted positively with the corresponding viable tumor cells, which demonstrated excellent preservation of H-2^b, EL4 tumor-specific, and G surface antigens. The H-2^b antigen on EL4 cells and the G surface antigens of E δ G2 cells, treated once with 0.1% formalin and stored at 4 C in Earle's balanced salt solution for 91 and 82 days, resp., were well preserved, which suggests that the formalin-treated tumor cells may provide a source of stabilized soluble antigens.

0909 IMMUNOCHEMICAL STUDIES ON MOUSE MYELOMA PROTEINS REACTIVE WITH DEXTRANS OR WITH FRUCTOSANS AND ON HUMAN ANTILEVANS.

(E.) Cisar, F. (Coll. Phys. Surg., Columbia U., New York, N.Y.), E.A. Kabat, J. Liao and M. Potter. *J Exp Med* 139(1):159-179, 1974.

Four BABL/c IgA mouse myeloma proteins (W3129, W3434, QUPC 52, and UPC 102) reactive with dextran, four myeloma proteins reactive with fructosans (three IgA (W3082, UPC 61, and Y5476), and one IgG2a (UPC 10)), and two human antilevans were studied immunochemically. Quantitative precipitin and inhibition assays showed that W3129, W3434, and QUPC 52 had specificities for isomaltose oligosaccharides similar to those previously found with α (1 \rightarrow 6)-specific human antidextran. W3129 and W3434 were most complementary to IM5, but W3129 reacted equally with IM4 and IM3, while W3434 had a greater affinity for IM4 and IM3. QUPC 52 had a larger combining region and was most complementary to IM6. Protein UPC 102 (IgA), like MOPC 104E (IgM), was most complementary to the α (1 \rightarrow 3)-linked trisaccharide, nigerotriose and thus differed from J558, which was inhibited best by nigeropentose. UPC 102 was similar to J558 but they differed from MOPC 104E in their reactions with the non- α (1 \rightarrow 3)-linked disaccharides. The fructosan-specific myeloma proteins fell into two groups with different specificities. The first group, including W3082 (IgA), UPC 61 (IgA), and the previously studied J606 (IgG3), reacted with

inulin and W3082; UPC 61 appeared to have identical specificities for β (2 \rightarrow 1)-linked fructofuranosyl residues with maximum complementarity for the tetrasaccharide β D-fructofuranosyl (2 \rightarrow 1) β D-fructofuranosyl (2 \rightarrow 1) β D-fructofuranosyl (2 \rightarrow 1)D-glucose, while protein J606 was inhibited best by the trisaccharide β D-fructofuranosyl (2 \rightarrow 1) β D-fructofuranosyl (2 \rightarrow 6)-glucose. W3082 and UPC 61 also differed from J606 in their behavior toward sucrose and β D-fructofuranosyl (2 \rightarrow 6) D-glucose as compared with α D-glucosyl (1 \rightarrow 3)D-fructose (turanose). The second group, containing myeloma proteins UPC 10 (IgG2a) and Y5476 (IgA), behaved similarly to the human antilevans in that neither reacted with inulin nor were they inhibited by the β (2 \rightarrow 1)-linked fructose oligosaccharides. Unlike the β (2 \rightarrow 1)-specific proteins, they reacted with perennial rye grass levan which contained over 90% β (2 \rightarrow 6) links. The differences in specificity and site size among homogeneous mouse myeloma proteins reactive with the same antigenic determinant are completely consistent with the concept that they represent products of homogeneous clones selected from the known heterogeneous population of antibody-forming cells.

0910 AUTOGENOUS IMMUNITY TO ENDOGENOUS RNA TUMOR VIRUS: CHRONIC HUMORAL IMMUNE RESPONSE TO VIRUS ENVELOPE ANTIGENS IN B6C3F₁ MICE. (E.) Batzing, B. L. (U. Tennessee-Oak Ridge Grad. Sch. Biomed. Sci.), M. Yurconic, Jr. and M. G. Hanna, Jr. *J Nat'l Cancer Inst* 52(1):117-131, 1974.

(C57BL/6 \times C3H/Anf δ)F₁ (B6C3F₁) mice were evaluated for immunologic reaction to endogenous murine leukemia virus (MuLV). By immunoelectron microscopy (IEM) it was demonstrated that throughout life these mice possess significant levels of free serum antibody specific for MuLV envelope antigen(s). Immunoglobulin and endogenous MuLV antigen(s), presumably in the form of immune complexes, became localized within kidney glomeruli with age; this deposition correlated well with the chronic development of glomerulonephritis. Immunoglobulin eluted from kidneys of aged animals also was shown by IEM to be specific for virus envelope antigen(s). Although the function of antibody in B6C3F₁ mice cannot be positively defined from these studies, it may be one critical component in the systemic regulation of levels of infectious endogenous leukemia virus.

0911 SUPPRESSION OF *IN VITRO* LEUKOCYTE MIGRATION IN CANCER PATIENTS BY MEANS OF AUTOLOGOUS AND HOMOLOGOUS TUMOR EXTRACTS. (Rus.) Novikov, D. K. (Vitebsk State Med. Inst., USSR) and G. D. Ademenko. *Dokl Akad Nauk SSSR* 217(3):715-718, 1974.

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CARCINOEMBRYONIC ANTIGEN. EARLY CLINICAL
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mission, Gif-sur-Yvette, France), F. Martin, J.
Guerin, R. Henry and C. Klepping. *Bull Cancer
(Paris)* 60(4):403-410, 1973.
- 0928 ASSAY OF ALPHA-FOETOPROTEIN. CLINICAL USE
OF RADIOIMMUNOASSAY. (Fr.) Masseyeff, R.
(Antoine-Lacassagne Ctr., Nice, France), B. P. Krebs,
J. P. Cassuto, C. Bonet, C. M. Lalanne and J. Delmont.
Bull Cancer (Paris) 60(4):383-392, 1973.
- 0929 " α_2 H GLOBULIN", A REACTIVE SERUM GLYCOPRO-
TEIN OF HEPATIC ORIGIN AND ITS RELATIONSHIP
TO MALIGNANT DISEASE. (Fr.) Rimbaut, C. (Inst Sci.
Res. Cancer, Villejuif, France). *Bull Cancer (Paris)*
60(4):411-420, 1973.
- 0930 *IN VITRO* ASSESSMENT OF CELL-BOUND IMMUNITY
TO A MURINE LEUKEMIA VIRUS. (E.)
Vathanaphas, K. (Albert Einstein Med. Ctr., Phila-
delphia, Pa.), E. G. Hampton and H. Friedman. *J
Reticuloendothel Soc* 15(6):11a, 1974.
- 0931 SPECIFICITY OF IMMUNE LYMPHOCYTES FOR *IN
VITRO* DETECTION OF TUMOR SPECIFIC TRANS-
PLANTATION ANTIGENS. (E.) Harris, L. F. (Sch. Med.,
Ohio State U., Columbus), V. V. Hamparian, J. H.
Hughes, H. G. Cramblett, E. A. Young and K. L.
Fowler. *J Reticuloendothel Soc* 15(6):12a, 1974.

0932 DEMONSTRATION OF CARCINOEMBRYONIC ANTIGENS (CEA), NONSPECIFIC CROSS-REACTING ANTIGENS (NCA) AND AN ASSOCIATED ALPHA PROTEIN IN NORMAL HUMAN TISSUES AND FLUIDS BY IMMUNODIFFUSION TECHNIQUES. (E.) Orjasaeter, H. (Natl. Inst. Public Hlth., Oslo, Norway). *Acta Pathol Microbiol Scand [B]* 82 (3):387-395, 1974.

See also:

- * (Rev): 0606, 0609, 0611
- * (Chem): 0619, 0663, 0691
- * (Viral): 0762, 0768, 0777, 0778, 0779, 0780, 0787, 0792, 0793, 0798, 0800, 0822

0933 IMMUNOLOGIC ASPECTS OF HUMAN INTRACRANIAL NEOPLASMS. (E.) Levy, N. L. (Duke U., Durham, N.C.). *Diss Abs Int B* 35(1):339-B, 1974.

- 0934 HISTOLOGY AND HISTOGENESIS OF EARLY GASTRIC CARCINOMAS WITH FLAT MUCOSAL ELEVATIONS. (E.) Nagayo, T. (Res. Inst., Aichi Cancer Ctr., Nagoya, Japan). *Acta Pathol Jap* 24(2):249-272, 1974.

Among 3828 histologically diagnosed cases of gastric carcinoma, were 648 cases involving growths which were still limited to the mucosa (m) or submucosa (sm). Of these early carcinomas, there were 36 cases of early gastric carcinomas with plateau-like sessile and flat elevations; 22 were restricted to the mucosa only, with 14 having shown invasion extending to the submucosa. Almost all of these elevated lesions had histological features of highly differentiated adenocarcinomas with well defined boundaries. With few exceptions, severe intestinal metaplasia was seen not only in the neighborhood of the elevated lesions but in the remaining antral mucosae. Well differentiated tubular adenocarcinomas appear to develop after such mucosae become malignant. The elevation of the lesions studied did not appear to be due to the primary growth of neoplastic tissue, but to the reactive growth of the nonmalignant mucosae, which was initiated by the development of the adenocarcinomas. The development generally occurs in the mucosae between the "area gastricae".

- 0935 PROLIFERATION OF PRENEOPLASTIC MAMMARY NODULE OUTGROWTH IN MAMMARY FAT PADS OF BALB/C MICE IN ORGAN CULTURE. (E.) Mehta, R. G. (Inst. Cellular Res., Sch. Life Sci., U. Nebraska, Lincoln), L. L. Washburn, P. N. Young, M. R. Banerjee and H. A. Bern. *J Natl Cancer Inst* 52(3):1013-1017, 1974.

Fragments of a murine mammary tumor virus (m-MTV)-free outgrowth of a hyperplastic alveolar nodule (HAN) from a BALB/c mouse (D₁ line) were transplanted into "gland-free" inguinal (fourth) mammary fat pads of BALB/c mice. Three weeks later, the whole mammary fat pad was removed and incubated in hormone-supplemented medium. Most of the outgrowth explants proliferated in the inguinal fat pad organ culture medium supplemented with the same hormones as are required for the *in vitro* growth of normal mammary gland; after 12 days, the nodule tissue filled over 50% of the fat pad. The extent of growth obtained within 12 days in organ culture was equivalent to that generally seen after 6 weeks *in vivo*. The rate of DNA synthesis in the explant corresponded with the growth pattern up to day 4; although DNA synthesis was reduced after this time, the explant continued to proliferate at a reduced rate up to 12 days. When the preneoplastic tissue was transplanted into already explanted fat pads, subsequent growth *in vitro* was not observed.

- 0936 THE CLINICAL SIGNIFICANCE OF CARCINOMA *IN SITU* OF THE BLADDER AND ITS ASSOCIATION WITH OVERT CARCINOMA. (E.) Skinner, D. G. (U. California, Sch. Med., Los Angeles), J. P. Richie, P. H. Cooper, J. Waisman and J. J. Kaufman. *J Urol* 112(1):68-71, 1974.

The incidence and distribution of carcinoma *in situ* (severe epithelial atypia) have been established in

a series of specimens from 59 patients (38 males and 21 females, aged 37-80 yr) undergoing radical cystectomy. Carcinoma *in situ* was most frequently seen in bladders containing grade 4 carcinoma. The highest incidence was documented adjacent to a neoplasm and a significant frequency was seen elsewhere in bladders containing a carcinoma. Carcinomas *in situ* were noted within the distal segment of the ureter or proximal segment of the urethra in 22 to 24% of the specimens studied. These data suggest that patients with diffuse carcinoma *in situ* or with alterations remote from an overt carcinoma should be managed by radical cystectomy and frozen section biopsy of ureteral and urethral margins. Partial cystectomy or segmental resection in such patients would seem to be contraindicated.

- 0937 A CLINICAL AND PATHOLOGICAL REVIEW OF OVARIAN STROMAL HYPERPLASIA AND ITS POSSIBLE RELATIONSHIP TO COMMON DISEASES OF THE FEMALE REPRODUCTIVE SYSTEM. (E.) Stearns, H. C. (Dept. Obstetrics Gynecol., Emanuel Hosp., Portland, Oregon), V. D. Sneed and J. D. Fearl. *Am J Obstet Gynecol* 119(3):375-379, 1974.

Corticostromal ovarian hyperplasia is generally found in the ovaries of women approaching or following menopause and appears to be associated with hyperestrogenism. Between 1969 and 1971, 383 women were admitted to a Portland, Oregon hospital with ovarian stromal hyperplasia; 141 were postmenopausal. Among the 383 cases studied, there was an inordinately high percentage of estrogen-dependent or estrogen-oriented pathologic entities. These entities included: 44 cases of endometrial carcinoma; 9 cases of markedly atypical endometrial hyperplasia; 17 cases of breast carcinoma; 11 cases of epithelial cervical carcinoma stage 0; 11 cases of leiomyosarcoma; and 28 cases of pelvic congestive syndrome. Of the 383 patients, 55.4% entered the hospital with complaints of abnormal bleeding. Thus, ovarian stromal hyperplasia appears to be associated with hyperestrogenism. The therapeutic addition of continuous estrogen medication (e.g., Premarin, Stilbestrol) unopposed by progesterone and given over a long period of time, may be a factor in promoting tumor growth.

- 0938 PATHOGENESIS OF A TRANSPLANTED CANINE LYMPHOCYTIC LEUKEMIA. (E.) Cohen, H. (Path. Res. Lab., VA Hosp., Kansas City, Mo.), A. L. Chapman, W. J. Bopp, C. E. Schmidt, C. E. Przybylski and M. S. McPhee. *Cancer* 33(5):1313-1324, 1974.

Eight neonatal beagles were inoculated s.c. with buffy coat cells of a canine lymphocytic leukemia maintained in serial passage in beagle neonates. The animals were killed 1, 2, 4, 7, 11, 16, 20, and 22 days after inoculation. The first appearance of lymphocytic neoplasm was noted on day 4 at the site of inoculation and in two regional lymph nodes. By day 11, leukemic cells had infiltrated other lymph nodes, the bone marrow, and the spleen. On day 16, the liver was infiltrated, and the peripheral blood was leukemic. These results suggest that the leukemic cells initially spread via the lymphatics to the lymph nodes and subsequently via the blood stream to

the bone marrow and spleen; the liver was involved secondarily to the spleen via the portal venous system. The peripheral blood did not contain large numbers of circulating neoplastic lymphocytes until after the bone marrow and spleen had already demonstrated considerable leukemic invasion. The finding of karyotypically female cells in a male recipient suggests that the leukemia was derived from the female donor and was therefore a transplant.

0939 ARGYROPHIL CELLS AND MELANOCYTES IN ESOPHAGEAL MUCOSA. (E.) Tateishi, R. (Ctr. Adult Dis., Osaka, Japan), H. Taniguchi, A. Wada, T. Horai and K. Taniguchi. *Arch Pathol* 98(2):87-89, 1974.

0940 THE CONTENT AND DISTRIBUTION OF NUCLEIC ACIDS IN THE EPITHELIUM OF THE UTERINE CERVIX IN ITS MALIGNIZATION. (Rus.) Kozachenko, M. A. (No affiliation). *Akush Ginekol (Mosk)* (12): 24-27, 1973.

0941 OSTEochondroma OF THE POSTERIOR CLINOID PROCESS. REPORT OF A CASE WITH SPECIAL REFERENCE TO ITS HISTOGENESIS. (E.) Ito, U. (Tokyo Med., Dental U., Japan), K. Hashimoto and Y. Inaba. *Acta Neuropathol (Berl)* 27(4):329-335, 1974.

0942 A SYSTEMATIC METHOD FOR THE DETECTION OF EXPERIMENTALLY INDUCED HYPERPLASIA AND EARLY NEOPLASIA IN THE URINARY BLADDER. (E.) Levin, S. (Dept. Pathol., U. Chicago, Ill.) and W. R. Richter. *Toxicol Appl Pharmacol* 27(3):680-684, 1974.

0943 SOME HISTOCHEMICAL PATTERNS OF CERVICAL CARCINOMA *IN SITU*. (It.) Frezza, M. (Reg. Hosp., Cittiglio, Italy). *Arch Ital Anat Istol Patol* 44(3/6):245-252, 1972.

0944 PRIMARY SARCOMAS OF THE MAMMELLA: ANATOMICAL AND CLINICAL CONSIDERATION OF 16 CASES. (It.) Polo, M. I. (Inst. Pathol. Anat. Histol., U. Bologna, Italy). *Arch Ital Anat Istol Patol* 44(3/6):215-243, 1972.

0945 THE PRESENCE OF NUCLEAR INCLUSIONS IN MALIGNANT TUMORS OF THE THYROID. (Fr.) Smejkal, V. (Endocrinol. Res. Inst., Prague, Czechoslovakia) and E. Smejkalova. *Rev Roum Endocrinol* 10(6):531-533, 1973.

0946 NEOPLASTIC DISEASE OF THE STOMACH IS NOT LIMITED TO CARCINOMA. (It.) Cacciari, C. (No affiliation), A. Marignani and P. Malaguti. *Boll Sci Med* 145(2):118-124, 1973.

0947 PATHOGENETIC MECHANISM OF THE PATTERN OF CELLULAR CHANGE IN MYELOPROLIFERATIVE SYNDROMES. (Ger.) Bakalos, D. (Evangelismos Hosp., Athens, Greece), M. Pararas, C. Pathouli and T. Tsikrikas. *Munch Med Wochenschr* 116(8):369-372, 1974.

0948 CANCER OF THE STOMACH AFTER GASTROENTEROSTOMY FOR ULCEROUS DISEASE. (Rus.) Mikhirev, I. V. (Provincial Oncol. Dispensary, Kalinin, USSR) and T. N. Mikhireva. *Vopr Oncol* 20(6):98-100, 1974.

0949 ABNORMAL PATTERNS OF MUCUS SECRETION IN APPARENTLY NORMAL MUCOSA OF LARGE INTES-TINE WITH CARCINOMA. (E.) Filipe, M. I. (Westminster Med. Sch., London, England) and A. C. Branfoot. *Cancer* 34(2):282-290, 1974.

0950 HISTOCHEMICAL FINDINGS ON PRELEUKEMIC STATES. (E.) Heller, A. (Med. Clin., Univ. Cologne, Germany) and R. Gross. *Blut* 28(6): 452-456, 1974.

0951 IDENTIFICATION OF PROMONOCYTES AND MONOCYTOID PRECURSORS IN ACUTE LEUKAEMIA OF ADULTS: ULTRASTRUCTURAL AND CYTOCHEMICAL OBSERVATIONS. (E.) Glick, A. D. (Vanderbilt U. Sch. Med., Nashville, Tenn.) and R. G. Horn. *Br J Haematol* 26(3):395-403, 1974.

0952 SCANNING ELECTRON MICROSCOPY OF THE HUMAN ENDOMETRIUM. II. HYPERPLASIA AND ADENOCARCINOMA. (E.) White, A. J. (U. Iowa Hosp., Iowa City) and H. J. Buchsbaum. *Gynecol Oncol* 2(1):1-8, 1974.

0953 A COMPARATIVE STUDY ON RAT LIVER AND HEPATOMA NUCLEAR MEMBRANES. (E.) Harris, J. R. (Bute Med. Bldg., St. Andrews, Fife, Scotland), M. R. Price and M. Willison. *J Ultrastruct Res* 48(1):17-32, 1974.

See also:

* (Chem): 0699, 0700, 0701
* (Imm): 0923

0954 THE VALIDITY OF RISK ESTIMATES OF LEUKEMIA
INCIDENCE BASED ON JAPANESE DATA. (E.)

Rossi, H. H. (Coll. Phys. Surg., Columbia U., New York, N. Y.) and A. M. Kellerer. *Radiat Res* 58(2):131-140, 1974.

On the basis of all available pertinent radiobiological evidence, it must be expected that the relative biological effectiveness of neutrons for the induction of human leukemia is a function of absorbed dose. An analysis of epidemiological and dosimetric data obtained at Hiroshima and Nagasaki has been found to conform to this expectation. Therefore, it must be concluded that the shapes of the dose-effect curves of the 2 Japanese cities are different and among the simplest assumptions that may be applied, a linear dose dependence for neutrons appears to be the most plausible. Risk estimates based on linear dependence for gamma radiation must, therefore, be excessive.

0955 MESOTHELIOMA REGISTER 1967-1968. (E.)

Greenberg, M. (Employment Med. Advisory Serv., Dept. Employment, London, England) and T. A. L. Davis. *Br J Ind Med* 31(2):91-104, 1974.

Between 1967 and 1968, 413 cases of mesothelioma were reported to the British Department of Employment, Medical Services Division. Of these cases, 246 were accepted as definite, 76 were considered definitely not mesothelioma, and the remainder were classified as "undecided" or "insufficient pathological material". Twelve percent of the definite mesotheliomas were of peritoneal origin. The ratio of mesothelioma in men and women was 5:1, which is similar to that for all malignant neoplasms of the respiratory system. The age range was 21-87 years, the mean age at death from mesothelioma being significantly younger than that for bronchial carcinoma and "all neoplasms". Of the confirmed cases, 167 had definite occupational exposure to asbestos, 29 were possibly exposed, and 38 had not been exposed. Among the remaining reported cases, nearly 1/3 were without apparent exposure and only 38% had a definite occupational history of exposure to asbestos. In 85% of the cases known to have been exposed to asbestos, death occurred more than 25 years after the first exposure; the interval between last handling asbestos and death was under 1 year in 40% of the cases. Definite cases of mesothelioma showed marked clustering in areas in which there was a substantial industrial use of asbestos. The observed annual incidence of definite mesotheliomas in England, Scotland, and Wales (120) may represent a considerable underestimation of the true prevalence.

0956 CLEAR-CELL ADENOCARCINOMA OF THE VAGINA AND
CERVIX IN GIRLS: ANALYSIS OF 170 REGISTRY
CASES. (E.)

Herbst, A. L. (Massachusetts Gen. Hosp., Boston), S. J. Robboy, R. E. Scully and D. C. Poskanzer. *Am J Obstet Gynecol* 119(5):713-724, 1974.

An analysis was made of 100 cases of vaginal and 70 cervical adenocarcinomas from the Registry of Clear-Cell Adenocarcinoma of the Genital Tract in Young Females. The patients ranged in age from 7 to 29 yr. Frequent exposure prenatally to diethylstilbestrol

and similar nonsteroidal estrogens was confirmed, the hormone being administered before the 18th week of pregnancy and continuing from 1 week to almost the entire length of the pregnancy. Dose ranged from 300 to 18,200 mg. Although most patients had vaginal bleeding or discharge, 16% were asymptomatic. Abnormal cytology was the first indication of cancer in 11 patients. However, 21% of the smears were negative. The larger and more deeply invasive tumors were often complicated by lymph node metastases, but these were also encountered in 1 case in which the tumor had an area of only 3 sq. cm and with another tumor that invaded less than 3 mm. These findings suggest that local treatment of the primary tumor alone may be inadequate in some cases. Recurrences developed in 37 of the patients and 24 of them died, although the follow-up in 1/3 of the patients was less than 2 yr. The recurrences frequently involved the lungs and supraclavicular lymph nodes as well as the pelvis. The very common association of vaginal adenosis and the occasional coexistence of transverse vaginal or cervical ridges provide morphologic evidence of a stilbestrol-related disturbance in the development of the lower Mullerian tract. Development of the urinary tract is not affected. The fact that all asymptomatic patients have been successfully treated demonstrates the importance of screening in these patients. The rarity (9%) of these cancers prior to the age of 12 yr suggest that the inclusion of a large population of girls in this age group in a screening program would result in the finding of a very few cases. However, such individuals should certainly be examined at any time abnormal vaginal bleeding or discharge develops.

0957 AETIOLOGICAL FACTORS IN OESOPHAGEAL CANCER
IN SINGAPORE CHINESE. (E.)

De Jong, U. W. (Unit Epidemiol. Biostat., IARC, Lyons, France), N. Breslow, J. G. E. Hong, M. Sridharan and K. Shammugaratnam. *Int J Cancer* 13(3):291-303, 1974.

Analysis of a hospital-based case-control study of esophageal cancer among Singapore Chinese (composed of various dialect groups including Cantonese, Hokkien, and Teochew) revealed the following statistically significant risk factors for both sexes: (1) belonging to either Hokkien or Teochew dialect groups; (2) consumption of beverages at very hot temperatures prior to illness; and (3) smoking Chinese cigarettes. Additional risk factors for males included birth in China and the consumption of Samsu (Chinese wine). Consumption of bread, potatoes, and bananas were at significantly lower levels in male esophageal cancer patients than in controls. Esophageal cancer was less common in males who attended school for more than 8 yr. Analysis of the joint influence of selected variables confirmed the strong effects of dialect group and beverage temperature for both sexes. For females the smoking of Chinese cigarettes remained a risk factor; for males, the consumption of Samsu. Smoking western-type cigarettes and consuming strong liquors were not significantly related for either sex. These findings suggest that esophageal cancer is more likely to occur among traditional Chinese who maintain dietary patterns which include Samsu and the drinking of beverages at hot temperatures, but avoid the bland

foodstuffs (bread, potatoes, and bananas) not native to their culture. The greater risk in Teochew and Hokkien may be due partly to consumption of a greater number of beverages at "burning hot" temperatures compared with Cantonese and other dialect groups. However, these differences are based on subjective impressions which should be verified by actual temperature measurements of drinks consumed.

- 0958 A SURVEY OF OCCUPATIONAL CANCER IN THE RUBBER AND CABLEMAKING INDUSTRIES: RESULTS OF FIVE-YEAR ANALYSIS, 1967-71. (E.) Fox, A. J. (Employment Med. Advisory Serv., Dept. Employment, London, England), D. C. Lindars and R. Owen. *Br J Ind Med* 31 (2):140-151, 1974.

The mortality rate from occupational cancer was studied among 40,867 35-65-year-old men employed in the rubber and cablemaking industries in Great Britain. The study was conducted between 1967 and 1971. In this group, there was a highly significant excess of deaths from all types of neoplasms, especially among those who began working after 1949 in factories using known carcinogenic compounds. There was also an excess number of deaths from bladder cancer among those exposed to known bladder carcinogens before 1950; no evidence was found for a continued excess risk of bladder cancer among people who entered the industry after that time. Among those involved in the production of tires, there was a significant excess of all neoplasms and of carcinoma of the bronchus. There was also an excess of carcinomas of the bronchus among those involved in the production of belting hose rubber with asbestos, and flooring. Those involved in the production of printing supplies showed a slight excess of neoplasms other than those of the bronchus and bladder. Neither smoking habits nor urban effects were likely primary causes of the observed excesses of bronchial carcinomas. Bronchial carcinomas were particularly common among tire industry employees involved in moulding, press and autoclave operation, the production of finished goods, stores, packing, and despatch, and among pan curemen. These results can be used only as an indication of problem areas and the type of further study required.

- 0959 EVIDENCE FOR SUPER-CRITICAL TUMOUR GROWTH. (E.) Williams, T. (Bristol U., England). *Adv Appl Probability* 6(2):237-238, 1974.

- 0960 ARSENIC CONTAMINATION OF DRINKING WATER AND FOODSTUFFS CAUSING ENDEMIC CHRONIC POISONING. (E.) Zaldivar, R. (Reg. Hosp., Antofagasta, Chile). *Beitr Pathol* 151(4):384-400, 1974.

- 0961 CANCER OF THE CERVIX: A SEXUALLY TRANSMITTED INFECTION? (E.) Singer, A. (Jessop Hosp. Women, Sheffield, England). *Lancet* (7871):41, 1974.

- 0962 STUDIES OF MITOTIC ACTIVITY OF ADENOCARCINOMATOUS CELLS IN THE RECTUM. (E.) Kalcheva, V. (Med. Acad., Plovdiv, Bulgaria) and M. D. Tileva. *Abdom Surg* 16(6):160-161, 1974.

- 0963 THE INCIDENCE OF CANCER AMONG IN-PATIENTS WITH AFFECTIVE DISORDERS. (E.) Evans, N. J. R. (Radcliffe Infirm., Oxford, England), J. A. Baldwin and D. Gath. *Br J Psychiatry* 124: 518-525, 1974.

- 0964 ANALYSIS OF CELL AGE DISTRIBUTION DURING ASCITES TUMOR GROWTH. (E.) Maruyama, Y. (U. Kentucky, Coll. Med., Lexington) and M. R. Raju. *J Natl Cancer Inst* 53(1):285-287, 1974.

- 0965 KINETICS AND THE FREE-RADICAL MECHANISMS OF TUMOR GROWTH. (E.) Emanuel, N. M. (Inst. Chem. Phys., Acad. Sci. USSR, Moscow). *Ann NY Acad Sci* 222:1010-1030, 1973.

- 0966 PERCOLATION PROCESSES AND TUMOUR GROWTH. (E.) Mollison, D. (King's Coll. Res. Ctr., Cambridge, England). *Adv Appl Probability* 6(2):233-235, 1974.

See also:

- * (Chem): 0628, 0691
* (Phys): 0740, 0742

- 0967 REGULATORY DEFECT OF GLYCOLYSIS IN HUMAN LIPOMA. (E.) Atkinson, J. N. C. (Dept. Biochem., U. Bristol, Great Britain), D. J. Galton and C. Gilbert. *Br Med J* 1:101-102, 1974.

The rates of lipogenesis, lipolysis, and glycolysis were studied in 23 lipomas removed from 23 patients; the lipomas were also assayed for phosphofructokinase. The lipoma extracts incorporated glucose-6-phosphate into glyceride-glycerol, but, unlike normal adipose tissue extracts, this could not be inhibited by the addition of citrate. Furthermore, the phosphofructokinase extracted from the lipomas was much less sensitive to inhibition by citrate than the enzyme of normal adipose tissue. The rates of conversion of glucose and palmitate to neutral lipid in the lipoma and adipose tissue was similar, as was the maximal rate of glycerol release and the rise in tissue levels of cyclic-AMP after stimulation with isoprenaline. The data suggest that a loss of negative feedback control over regulatory enzymes may be an early feature in the development of neoplasia.

- 0968 INDUCTION, DIFFERENTIATION AND ONCOGENESIS. (E.) Wheldon, T. E. (Western Reg. Hosp., Glasgow, Scotland) and J. Kirk. *J Theor Biol* 41:261-268, 1973.

Eukaryotic cytodifferentiation usually leads to stable end-states. However, evidence on embryonic induction in amphibia supports the view that the initial stages of cellular maturation following induction of differentiation are comparatively labile, stability being a property acquired during maturation. Early developing cells may therefore retain the capacity for reversion to their previous, less developed, condition and a proportion of any group of induced cells may do so. Possible implications of such a phenomenon are explored, using two kinetic models of reversion. It is concluded that reversion is a possible mechanism in leukemogenesis and other forms of oncogenesis.

- 0969 GENE ACTIVATION IN EUKARYOTES: ARE NUCLEAR ACIDIC PROTEINS THE CAUSE OR THE EFFECT? (E.) Pederson, T. (Worcester Fdn. Exp. Biol., Shrewsbury, Mass.). *Proc Natl Acad Sci USA* 71(3): 617-621, 1974.

To determine whether nuclear acidic proteins play a role in the positive control of gene transcription in eukaryotes, the amounts of pulse-labeled acidic protein were measured in the chromatin and ribonucleoprotein containing heterogenous nuclear RNA (hnRNP) of normal and hormone activated rat liver. When the synthesis of rat-liver heterogenous nuclear RNA (hnRNA) was stimulated by the administration of hydrocortisone, there was a parallel increase in the labeling of the acidic proteins in the hnRNP. However, there was no detectable effect on the labeling of the acidic chromatin proteins or histones. Thus, the nuclear acidic proteins that respond to the hormone are concerned with a post-transcriptional event, namely the assembly and pro-

cessing of hnRNP, rather with direct gene activation. Previously observed increases in the synthesis of "chromatin" acidic proteins during gene activation may reflect the presence of these ribonucleoprotein particles in crude chromatin preparations.

- 0970 A DIFFUSIBLE FACTOR RESTORING CONTACT INHIBITION OF GROWTH TO MALIGNANT MELANOCYTES. (E.) Lipkin, G. (Dept. Path., U. Zurich, Switzerland) and M. E. Knecht. *Proc Natl Acad Sci USA* 71(3):849-853, 1974.

Saturated cultures of a highly malignant hamster amelanotic melanoma cell line (RPMI no. 1846) and the contact-inhibited blue nevus-transformed (FF) line which arose from it were grown in growth medium without serum. The cells were then centrifuged, lyophilized, and analyzed by polyacrylamide gel electrophoresis and column chromatography. The FF cell line was found to have a diffusible protein-containing factor of high molecular weight which was not present in the RPMI no. 1849 cells. This factor contained deoxyribose, but no virus particles were detected. Cultures of RPMI no. 1846 cells grown with this factor exhibited contact inhibition of growth similar to that found in cultures of FF cells. Prior treatment of the factor with DNase had no effect on contact inhibition, while prior treatment with Pronase completely prevented it. The appearance of increased numbers of fibroblast-like cells among the RPMI no. 1846 cells (rounded or dendritic melanocytes when grown in the absence of the factor) preceded actual contact between the cells, but the number greatly increased following such contact. The changes in the RPMI no. 1846 cells were completely reversible following the removal of the factor from the growth medium. The activity of the factor was preserved in aqueous solutions at 4 C for at least 8 weeks, but was destroyed by repeated freeze-thawing. The contact-inhibitory factor may be the prototype for a fundamental mammalian cellular mechanism for the regulation of normal cell-to-cell contact interactions.

- 0971 WALKER 256 TUMOR IMPLANTATION IN NORMAL AND INJURED PERITONEUM STUDIED BY ELECTRON MICROSCOPY, SCANNING ELECTRON MICROSCOPY, AND AUTORADIOGRAPHY. (E.) Buck, R. C. (Dept. Anat., Health Sci. Ctr., U. Western Ontario, London, Canada). *Cancer Res* 33(12):3181-3188, 1973.

The localization of Walker 256 tumor cells introduced into the peritoneal cavity of female Sprague-Dawley rats with intact peritonea and peritonea which had been denuded of mesothelial cells was studied by transmission electron microscopy (TEM), scanning electron microscopy (SEM), and autoradiography. TEM showed no changes in the mesothelium of the unoperated tumor-bearing animals up to 3 days after tumor cell injection; on the fourth and fifth days, the mesothelial cells changed their shape. Only two specimens showed tumor cells, both 5 days after injection. These observations were confirmed by SEM and autoradiography. In the tumor-bearing animals with peritonea denuded of mesothelial cells, TEM

showed large numbers of cells with the characteristics of Walker tumor cells as early as 2 hours after tumor cell injection. Both the tumor cells and macrophages were adherent to the wounded area. At later stages, the tumor cells greatly increased in number, forming a continuous sheet sometimes several cells thick. The macrophages appeared to have been crowded out by the growth of the tumor cells. By the fifth day, the tumor cells had invaded the underlying connective tissue. These observations were confirmed by SEM and autoradiography.

0972 MAMMARY CARCINOMA IN THE CAT: A MODEL IN COMPARATIVE CANCER RESEARCH? (E.) Weijer, K. (Netherlands Cancer Inst., Amsterdam), J. F. Hampe and W. Misdorp. *Arch Chir Neerl* 15(4):413-425, 1973.

A description is given of the morphology and biological behavior of 179 malignant mammary tumors in 170 cats. The tumors were found in all glands, but were significantly less frequent in L2 and L3. The series consisted of 114 intact females, 40 ovariectomized females, and 2 castrated males. The average at which the tumors were detected was 10.8 years and the mean duration of survival after detection was 12.3 months. The poor prognosis was probably related to the delay between detection and surgery (mean 7 months), and there was a positive correlation between the 1-year survival rate and the volume of the tumor at detection. Metastases were encountered in 120 of the 129 animals autopsied, mostly in the lungs (83.6%), regional lymph nodes (82.8%), pleurae (42.2%), and liver (23.6%). Histologically, there were 53 tubular adenocarcinomas, 52 papillary adenocarcinomas, 35 solid carcinomas, two mucoid carcinomas, 34 compound carcinomas, and three sarcomas. About 50% of the low-grade malignancy group survived for longer than 1 year, while only 10% of the high-grade malignancy group survived that long.

0973 HEPATOMA - FOETAL PHE-tRNA ALSO PRESENT IN NORMAL RAT LIVER. (E.) Mushinski, J. F. Natl. Cancer Inst., Bethesda, Md.). *Nature* 248(5446):32-334, 1974.

Using RPC-2 chromatography, two isoaccepting species of Phe-tRNA have been found in rat hepatomas, with only one being found in normal rat liver. Similar results were obtained using another reversed phase column system, RPC-5. However, the earlier eluting peak (not formerly seen in normal liver) was more prominent using RPC-5 chromatography and tRNA aminoacylated with G-10 enzymes than with RPC-2 chromatography of tRNA aminoacylated with DEAE enzyme. Furthermore, normal liver tRNA aminoacylated using the G-10 enzyme showed the presence of a prominent peak of Phe-tRNA which was not seen when the DEAE enzyme preparation was used. Mixtures of DEAE and G-10 enzyme preparations yielded Phe-tRNA identical in amount and pattern to that produced by G-10 enzyme alone. It is possible that the previously reported abundance of the early-eluting Phe-tRNA peak in fetal rat liver may also be associated with a great abundance of that activity found deficient in the DEAE enzyme but abundant in the G-10 preparations.

0974 THE DEVELOPMENT OF TERATOMAS FROM PARTHENOGENETICALLY ACTIVATED OVARIAN MOUSE EGGS. (E.) Stevens, L. C. (Jackson Lab., Bar Harbor, Me.) and D. S. Varnum. *Dev Biol* 37(2):369-380, 1974.

Ovarian teratomas developed spontaneously in about half of the females of an inbred colony of LT mice. Some of the tumors began to develop at about 30 days of age, the incidence rising to about 50% in animals 90 days of age. The tumors originated from ovarian eggs which began to develop parthenogenetically. They resembled normal embryos until the blastocyst stage, after which most became disorganized. The most advanced ovarian embryo observed had a primitive streak and resembled a normal embryo of 7.5 days gestation. Most of the teratomas were benign and composed of many types of well differentiated tissues of embryonic and extraembryonic origin, but some of them contained proliferating undifferentiated cells. Parts of many of them were grafted s.c. into syngeneic hosts, but only one gave rise to a transplantable teratoma. It produced several tissue types and undifferentiated stem cells. Parthenogenesis also occurs spontaneously in a small percentage of ovulated LT eggs. They undergo cleavage and implant in the uterus. Most of them die at 5-7 days of gestation.

0975 EFFECT OF AN INTERSTITIAL GLAND TUMOR OF TESTICULAR ORIGIN ON RECEPTOR ORGANS IN THE FETAL RAT. (Fr.) Pourreau-Schneider, N. (Lab. Exp. Embryol., Coll. France, Paris). *Ann Embryol Morphogenesis* 6(1):63-80, 1973.

The effect of an interstitial gland tumor on sex differentiation was studied in fetal Wistar rats. This tumor was first induced in the testes of albino Wistar Glaxo rats by prolonged treatment with serum gonadotropin from a pregnant mare, and the tumor was maintained by s.c. grafting in rats. When suspensions of these tumor cells were injected i.p., i.v., or into both uterine horns of pregnant rats, sex differentiation on their offspring was normal. Similarly, ovaries and testicles from fetal rats (14 1/2-8 1/2 days old) showed no evidence of abnormal development when they were grafted *in vivo* in intact or castrated rats under the connective tissue capsule surrounding the tumor. Oocytes from younger embryos (14 1/2-15 1/2 days old) failed to survive. If fetal gonads were explanted at the onset of differentiation and cultivated *in vitro* with the tumor, testes developed better than controls which were grown in a medium containing no hormones. The interstitial gland tumor stimulated tubular development and maintained spermatogenesis. When ovaries were explanted before morphological differentiation had begun, 28 developed normally and 13 others formed medullary structures of the tubular type in the presence of the tumor. Cortical development was not inhibited and oocyte meiosis was not prevented. Analogous results were obtained when the experimental period was extended by grafting fetal gonads into the coelom of a chick embryo and incubating them with interstitial gland tumor. Since the tumor did not inhibit development of the paramesonephric duct in the male genital tract it is not capable of replacing the testes in sex differentiation. In the undifferentiated female genitalia both the tumor and the fetal testes maintained the

mesonephric ducts and induced development of the epididymis, seminal vesicles, and prostate anlagen.

- 0976 CYTOPHOTOMETRIC INVESTIGATIONS OF THE DEOXY-RIBONUCLEIC ACID AND NUCLEOHISTONE CONTENTS OF SQUAMOUS CELL CARCINOMAS OF THE SKIN AND TRANSITIONAL MUCOSA WITH DIFFERENT DEGREES OF DIFFERENTIATION. (Ger.) Ehlers, G. (Dermatol. Clin., Technical U., Munich, Germany) and I. Herbstreit. *Arch Dermatol Forsch* 247(2):125-144, 1973.

By using Feulgen and Fast Green staining, the DNA and nucleohistone contents and ploidy were investigated in 20 squamous cell carcinomas of the skin or lips. Human diploid cells (thymus lymphocytes) were used as controls. In most of the carcinomas studied the mean DNA content was twice that in thymus lymphocytes and the mean nucleohistone content was 2-4 times higher. Of 4 highly keratinized tumors, 3 had DNA patterns in the triploid or hypertetraploid range; the remaining tumor had a diploid stemline. DNA maxima in the hypertetraploid, triploid, or hypertetraploid range were observed in 8 of 9 partially keratinized squamous cell carcinomas. The remaining tumor had a hypertetraploid DNA stem line. Three undifferentiated squamous cell carcinomas also had DNA maxima in the triploid range. Similar results were obtained on a tumor that had developed from a crural ulcer and on two of three tumors which developed after exposure to x-rays or γ -radiation. A DNA maximum in the hypertetraploid range was found in one tumor which recurred after γ -radiation. A comparison of DNA and nucleohistone histograms showed no differences between squamous cell carcinomas which varied in the extent of their differentiation.

- 0977 BLOOD COAGULATION ABNORMALITIES IN CHRONIC MYELOID LEUKEMIA. (E.) Mandelli, F. (Inst. Med. Semeiotics, U. Rome, Italy), S. Amadori, G. Gandolfo, G. Isacchi, G. Mariani, G. Papa, S. Pisarri and F. Salsano. *Haematologica* 57(11):686-696, 1973.

Blood coagulation, platelet function, and platelet survival were studied in 17 patients with chronic myeloid leukemia (CML). Nine patients were examined during the active phase of the disease, eight were studied during remission, and five were studied before and after treatment. Whole blood clotting tests were normal in all cases, although from thromboelastograms MA was increased in six cases and r and k were prolonged in two cases. The partial thromboplastin was prolonged in two cases, prothrombin consumption was decreased in seven cases, a reduction of the prothrombin complex factors was recorded in some cases, and Factor VIII was often increased. Factor IX was nearly always in the normal range. Bleeding time was normal in all cases. The platelet level was increased in three of nine patients prior to treatment and 2 of 13 patients during remission. Fibrinolysis was normal, and fibrinogen was nearly always normal. The plasminogen level was decreased in four patients before treatment and was normal after treatment. Fibrinogen degradation products were increased in about 1/3 of treated and untreated patients. Platelet aggregation was frequently abnormal before treatment, and was frequently reduced after treatment. PK and

LDH activities were increased in untreated patients to treated patients. Platelet survival was normal.

- 0978 COMPARATIVE STUDY OF THE INCORPORATION OF ^{32}P INTO THE PHOSPHOLIPIDS OF MEMBRANES FROM NOVIKOFF HEPATOMA ASCITES CELLS AND LIVER CELLS FROM NORMAL AND TUMOR BEARING ANIMALS. (E.) Anghileri, L. J. (GHS Clin., Essen, Germany). *Z Krebsforsch* 80(4):301-306, 1973.

The incorporation of ^{32}P into the phospholipids of the membranes and cells of the ascitic Novikoff hepatoma and the livers of normal and tumor bearing male Holtzman rats was studied. The membranes of the ascites cells showed a lower percentage of total ^{32}P incorporation into the lipid fraction than did the liver cell membranes, whereas the ^{32}P specific activity of that fraction was much higher in the ascites cells. In addition, the phosphorus content of that fraction was lower than in the corresponding fraction of the liver cells. The TCA-soluble fraction contained more ^{32}P and showed a very high specific activity, with the KOH-soluble fraction showing a similar pattern. In all of the membranes, the higher phosphorus content was observed in the lipid fraction. The incorporation of ^{32}P into the various phospholipids did not differ significantly among the membranes of the various cell types. The results indicate that the metabolic rate in the phospholipid fraction is higher in tumor cells and liver cells from tumor bearing animals than in liver cells from nontumor bearing animals. In addition, the tumor cells appear to exhibit a very high turnover rate for low molecular weight phosphorylated molecules.

- 0979 ENHANCEMENT OF TUMOR GROWTH AND METASTASES BY MEDROXYPROGESTERONE ACETATE IN TRANSPLANTED UTERINE ADENOCARCINOMA CELLS OF THE RAT. (E.) Sekiya, S. (Dept. Obstetrics Gynecol., Chiba U. Sch. Med., Japan), A. Yano and H. Takamizawa. *J Natl Cancer Inst* 52(1):297-298, 1974.

High- (HTP/C1) and low- (LTP/C3) tumorigenic cloned cells of 7,12-dimethylbenz(a)anthracene-induced Sprague-Dawley rat uterine adenocarcinoma were injected s.c. into the interscapular region of isologous newborn rats within 48 hours after birth. Some animals were then given twice weekly s.c. injections of 0.5 mg medroxyprogesterone acetate for 5 weeks beginning 2 weeks after cell inoculation. The HTP/C1 cells produced progressively growing tumors in all newborn rats. The tumors grew slowly during the first 2 weeks then exhibited exponential growth. Many of these tumors metastasized to the lung, and thoracic and peritoneal cavities. Most of the rats inoculated with the LTP/C3 cells developed slowly growing tumors which occasionally regressed without metastasis to the lung. Histologically, the tumors produced by both types of cells were moderately undifferentiated adenocarcinomas. The tumors produced in the female rats were significantly larger than those produced in the males regardless of treatment with medroxyprogesterone acetate or the tumorigenicity of the inoculated cells. Medroxyprogesterone acetate enhanced tumor growth in the LTP/C3-inoculated rats but not in the

HTP/C1-inoculated rats, and the enhancement was not influenced by sex. Medroxyprogesterone acetate enhanced metastasis to the lung in LTP/C3-treated animals, the metastatic frequency being slightly higher in females than males. Metastases to the kidney and/or heart were found only in LTP/C3-inoculated animals treated with medroxyprogesterone acetate. Progesterone may act immunosuppressively *in vivo* or make alterations in the environmental conditions of the tumors.

0980 EFFECT OF THE CYTOSTATIC, BLEOMYCIN, ON THE QUANTITATIVE CELL ARCHITECTURE OF RAT LIVER CELLS. (Ger.) Riede, U. N. (Inst. Pathol., U. Basel, Switzerland), W. Kaiser, C. von Matt and H. P. Rohr. *Z Krebsforsch* 80:323-334, 1973.

Electron microscope examinations were made of livers from 3 male Wistar rats given bleomycin (2.5 mg/100 g/day i.p. for 3 days) and those from 3 untreated rats. In bleomycin-treated rats some of the rough endoplasmic reticulum was dilated and contained vesicles. The compartment volume and membrane surface of the rough endoplasmic reticulum decreased by 33%. Ribosomes not attached to membranes made up a significantly larger proportion of the cytoplasm. These free ribosomes were often present as semicircular or spiral polysomes. The number of microbodies per unit volume cytoplasm decreased by 1/3, and the volume of each microbody decreased significantly. The volume of lysosomes per unit volume cytoplasm also decreased by 1/2. These findings indicate that bleomycin impairs protein synthesis in the rat liver, but adaptive reactions occur to compensate for this.

0981 CORTICAL CONTROL OF CELL DIVISION. THE CELL SURFACE APPEARS TO DETERMINE SOME SPECIFIC EVENTS OF DIVISION IN STENTOR AND EGG CELLS. (E.) De Terra, N. (Fox Chase Ctr. Cancer Med. Sci., Philadelphia, Pa.). *Science* 184(4136):530-537, 1974.

In both *Stentor* and egg cells cortical changes may control the time of cell division and the cortex may be involved in determining certain events in the replication of the nucleus and centrioles or basal bodies. Increasing evidence suggests that the cell surface plays a major role in controlling the division of mammalian cells. Experimental studies on amphibian and marine invertebrate eggs have led to similar conclusions and therefore provide a bridge between the work on *Stentor* and the work suggesting control of cell division by the cell surface in the mitotic divisions of mammalian cells. Mitotic abnormalities or organelle replication in tumor cells may well prove to be a consequence of abnormal surface structure. Some of these phenomena cannot be adequately explained by mechanisms involving propagated structural changes.

0982 TUMOR-HOST CELL HYBRIDS IN RADIOCHIMERAS. (E.) Wiener, F. (Karolinska Inst., Stockholm, Sweden), E. M. Fenyo and G. Klein. *Proc Natl Acad Sci USA* 71(1):148-152, 1974.

F₁ hybrid mice syngeneic or semiallogeneic with re-

spect to the relevant tumor were lethally irradiated and then reconstituted with hemopoietic cells from strain CBAT6T6 mice. The animals were inoculated with solid or ascites tumors after chimerism had been established. Tumor-host cell hybrids were selected from enzyme-deficient solid tumors by explanting the tumor cell suspension into hypoxanthine-amethopterin-thymidine containing medium. The selection of hybrid cells from ascites tumors was achieved by exploiting the difference between the ascites tumor cells and hybrid cells in their ability to adhere to the surface of culture vessels. T6T6 chromosomal and H-2 antigenic markers served to distinguish between hemopoietic cells derived from the donor graft and cells of the host. All solid tumors fused with cells of the irradiated host, whereas ascites tumors fused with repopulating cells of hemopoietic origin. It is suggested that the most likely cell type to be involved in the fusion would be a macrophage type. The difference in partner preference concerning the fusion pattern between solid and ascites tumors may arise from differences in the origin of fixed and free macrophages in the radiation chimeras.

0983 COLON CANCER AND BLOOD-CHOLESTEROL. (E.) Bjelke, E. (Cancer Registry Norway, Oslo). *Lancet* (7866):1116, 1974.

Blood cholesterol levels among a subsample of Norwegian men aged 41-76 years were negatively correlated with reported intake of processed meats and positively correlated with coffee intake. Dietary histories from Norwegian gastrointestinal cancer patients and controls indicated that the frequency of consumption of processed meats was positively associated with colonic cancer, while coffee intake was negatively associated with colonic cancer. Analyses of a 5-year follow-up of persons involved in a prospective study of dietary habits indicated that the risk of colonic cancer among persons eating processed meats 14 or more times per month was particularly high. The blood cholesterol differential increased when the intakes of processed meats and coffee were considered together. Low-meat, high-coffee intakes were associated with high cholesterol levels and low-risk of colonic cancer, while high-meat, low-coffee intakes were associated with low cholesterol levels and higher risk of colonic cancer. Processed meats seem to increase the risk of colonic cancer mainly by interacting with coffee. The relationship between processed meat intake and cancer appears to apply to all large-bowel cancers. Factors which could modify the effects of a high-fat intake should be considered when assessing the risk of colonic cancer.

0984 PROGESTERONE METABOLISM BY PROLIFERATIVE AND SECRETORY HUMAN ENDOMETRIUM. (E.) Collins, J. A. (Dept. Obstetrics Gynecol., U. Western Ontario, London, Canada) and D. M. Jewkes. *Am J Obstet Gynecol* 118(2):179-185, 1974.

Proliferative and secretory human endometrium samples were incubated with progesterone-¹⁴C and NADPH. Five products of endometrial metabolism were detected, 5 α -pregnan-3,20-dione (the major product of proli-

ferative incubations); 20 α -OH-pregn-4-en-3-one (the major product of secretory incubation); two unidentified steroid carriers; and an unidentified compound with an Rf of 0.48. Conversion to each steroid product was linear with time up to 30 minutes, and all five products accumulated uniformly. It is unlikely that progesterone concentrations in the endometrial tissues influenced the pattern of enzymatic metabolism, and the progesterone concentration in the incubation medium was ruled out as a rate-limiting factor in the conversion of steroid metabolites. The results suggest that the functional and histologic changes which occur in the endometrium after ovulation are associated with potential changes in progesterone metabolism. The importance of Δ^4 -5 α -dehydrogenase appears to decline in favor of Δ^4 -20 α -dehydrogenase in the postovulatory endometrium, although it is unclear whether either activity facilitates any specific gestational event.

- 0985 CHROMOSOME STUDIES IN TWELVE PATIENTS WITH RETINOBLASTOMA. (E.) Czeizel, A. (Lab. Human Genetics, Natl. Inst. Public Health, Budapest, Hungary), L. Csosz, J. Gardonyi, L. Remenar and P. Ruzsicka. *Humangenetik* 22:159-166, 1974.

Blood leukocytes from 12 children (3-11-years-old) with retinoblastoma and 15 normal children were examined for chromosomal abnormalities. The frequency of aneuploid cells without polyploid metaphases was higher among the diseased children than among the controls, as was the frequency of cells with 45 and 47 chromosomes. The frequency of chromatid-type aberrations was also significantly higher among the children with retinoblastoma. The frequency of unstable aberrations of the chromosome type was similar in the two groups, while the number of stable aberrations of the chromosome type was significantly higher among the diseased children. A similar increase in the occurrence of chromosome abnormalities was found in cases of retinoblastoma not exposed to therapeutic irradiation. These findings indicate retinoblastoma patients exhibit an increased chromosomal fragility which may be associated with a general increase in the predisposition to tumor development.

- 0986 TRANSFORMATION OF HUMAN FIBROBLASTS WITH D.N.A. OF CULTURED HUMAN RHABDOMYOSARCOMA CELLS. (E.) Karpas, A. (Dept. Med., U. Cambridge, England) and E. Tuckerman. *Lancet* (7867):1138-1141, 1974.

DNA was extracted from human rhabdomyosarcoma cells which had been maintained in culture for over 2 years and which exhibited an abnormal growth pattern, pleomorphic cytology, and highly abnormal karyotypes. Cultured human fibroblasts derived from the skin of a normal fetus were incubated with the DNA preparation, after which all cells were prepared for karyotype analysis. After repeated subculturing for 8 months, the uninfected control fibroblasts ceased growing, while the DNA-infected cultures continued to grow rapidly to form dense multilayers. After 6 months, the control fibroblasts exhibited normal

karyotype, while 7.5% of the DNA-treated cells had abnormal karyotypes with chromosomal rearrangements, endoreduplications, breaks, and acentric and dicentric chromosomes. Karyotype analysis of the original rhabdomyosarcoma cells revealed multiple breaks, endoreduplication, chromosomal rearrangements, polyploidy, and the presence of abnormal marker chromosomes. These data indicate that DNA from malignant human cells may provide a promising approach for the eventual isolation of the etiological agents involved in the development of human sarcoma and leukemia.

- 0987 WATER CONTENT AND PROTON SPIN RELAXATION TIME FOR NEOPLASTIC AND NON-NEOPLASTIC TISSUES FROM MICE AND HUMANS. (E.) Inch, W. R. (Ontario Cancer Treatment Res. Fdn., London, Canada), J. A. McCredie, R. R. Knispel, R. T. Thompson and M. M. Pintar. *J Natl Cancer Inst* 52(2):353-356, 1974.

The spin-lattice relaxation times (T_1) of normal and malignant tissues from 71 C3H/HeJ and CFWD mice and eight humans were measured; in mice, values were longer for malignant than normal tissues. Liver, spleen, and kidneys from animals with large, rapidly growing tumors had longer T_1 values than similar tissues from normal animals. There was no increase in T_1 for nonmalignant tissues from animals with large, slow-growing tumors. T_1 were related to tissue water content. Fetal and regenerating liver had longer T_1 values than normal liver. T_1 are not likely to be of value in the diagnosis of cancer in an early stage.

- 0988 "DOMES", PERIODICALLY EXPANDING AND COLLAPSING SECRETORY STRUCTURES IN CELL CULTURES OF MOUSE MAMMARY TUMORS. (E.) Visser, A. S. (Dept. Path., Wilhelmina Gasthuis, U. Amsterdam, The Netherlands) and F. J. A. Prop. *J Natl Cancer Inst* 52(1):293-295, 1974.

Monocellular suspensions made from primary mammary tumors of C3H mice bearing the mammary tumor virus (MTV) formed domes approximately 1 day after the cultures formed confluent epithelial monolayers. These domes were studied using time-lapse microcinematographic phase contrast movies. The domes expanded and collapsed 1-4 times every 2 hours in untreated cultures and cultures treated with: insulin, prolactin, and cortisol; insulin, progesterone, and cortisol; and progesterone and cortisol. During expansion, the dome gradually filled itself with fluid following the initial release of a small area of cells from the underlying polystyrene bottom. The adherent cells at the margin often suddenly loosened and became part of the dome surface structure. The growth of the dome continued for 30-120 minutes, after which the dome emptied itself within 2 minutes. For 4-15 minutes thereafter, the dome cells were barely discernible from the surrounding monolayer cells. Then the cycle repeated itself. New domes in time originated in places where a "quiescent" monolayer previously existed. In some domes during filling, certain solitary cells consistently remained attached to the bottom. The pulsations in the domes are most easily explainable in terms of

secretory activity of the dome cells into the dome cavity followed by rupture of the intercellular connections when the tension in the dome became too high.

- 0989 A UNIQUE SERUM PROTEIN IN MICE WITH VARIOUS TUMORS. (E.) Palmer, W. G. (Nat'l. Cancer Inst., Frederick Cancer Res. Ctr., Md.), T. W. Orme and C. W. Boone. *J Nat'l Cancer Inst* 52(1):279-282, 1974.

Serum samples from different strains of mice with 10 different types of transplantable tumors were examined by immunosorption coupled with polyacrylamide electrophoresis. A unique protein band was observed in numerous serum samples from mice carrying all types of tumors except the Rauscher leukemia virus-induced lymphoid tumor. The detection of this tumor-bearer serum protein (TBSP) on acrylamide gels was facilitated by the prior immunosorption of serum with Sepharose-linked antiserum to normal adult mouse serum proteins. TBSP was not observed in any normal serum sample, and in the tumor-bearing samples it varied in quantity with the tumor type and the stage of tumor development. Sera from fetuses and hepatectomized mice were all TBSP negative. The development of mouse TBSP was correlated with tumor growth. Surgically cured mice were negative for TBSP 3 months after surgery. TBSP did not appear in normal mice following the induction of granulomas by the s.c. inoculation of Freund complete adjuvant. Although TBSP may be related to a protein known as the acute phase of α_2 -AP-globulin it may differ from the acute phase protein.

- 0990 TUMOR GROWTH AND NEOVASCULARIZATION: AN EXPERIMENTAL MODEL USING THE RABBIT CORNEA. (E.) Gimbrone, M. A., Jr. (Children's Hosp. Med. Ctr., Boston, Mass.), R. S. Cotran, S. B. Leapman and J. Folkman. *J Nat'l Cancer Inst* 52(2):413-427, 1974.

Fragments of homologous tumors--Brown-Pearce epithelioma and V2 carcinoma--were implanted into the avascular corneal stroma of New Zealand white rabbits at various distances from the limbus. Tumor growth and neovascular response of limbal vessels were studied by: 1) slit lamp stereomicroscopy, 2) histologic examination, 3) filling of vasculature with colloidal carbon, and 4) autoradiography after exposure to ^3H -thymidine. Centrally placed tumors spread as thin plates until they reached within 2.5 ± 0.5 mm of the limbus, when new vessels began to grow from the limbal plexus toward the tumor edge. When tumors became vascularized, they grew rapidly into exophytic masses. Peripherally placed tumors evoked early neovascularization. The prevascular growth of incompatible rabbit homograft and mouse xenograft tumors suggested that the cornea, before its vascularization, was an immunologically privileged site for tumor growth. Intracorneal polyacrylamide gel implants containing tumor extracts elicited a specific pattern of corneal vascularization not observed with nonmalignant cell extracts. These experiments provide a new model for study of tumor growth and neovascularization in a site where there is anatomic

separation of tumor cell stimulus from host vascular response; the technique of corneal gel implantation may be useful in the characterization of mediators of neovascularization.

- 0991 CHROMOSOME BANDING PATTERNS IN EHRlich AND YOSHIDA ASCITES TUMORS. (E.) Sasaki, M. (Fac. Sci., Hokkaido U., Sapporo, Japan), M. Mori and M. Oshimura. *J Nat'l Cancer Inst* 52(4):1307-1315, 1974.

Chromosomal banding patterns of the hyperdiploid Ehrlich mouse carcinoma (EC) and the Yoshida rat sarcoma (YS) were studied by the quinacrine fluorescence and Giemsa banding methods. The banded karyotypes of both tumors deviated greatly from those of normal somatic cells of host animals. Although most EC cells possessed 43 chromosomes including 1 A, 2 B, and 3 m markers, the banded profile of the karyotype was highly variable. There were usually 26 abnormal elements in which the origin was untraceable even with banding analysis. Of the remaining 17 elements, 14 exhibited apparently normal morphology with normal banding patterns, whereas three showed partially normal patterns. The stemline cells of YS had 40 chromosomes, 12-13 apparently normal and 27-28 structurally altered elements. Among the abnormal elements, nine were traceable either totally or partially. The cell population of YS was more homogeneous than that of EC.

- 0992 INTERACTION OF SPERM WITH SOMATIC CELLS. (E.) Coppleson, M. (Queen Elizabeth II Res. Inst. Mothers Infants, U. Sydney, Australia) and B. L. Reid. *Science* 185(4146):104, 1974.

Based on evidence that human cervical cancer is truly venereal and on the demonstrable intimacy of the nucleic acids of the sperm head and the cervical epithelial cell following coitus, it was proposed nearly a decade ago that the male gamete might be a vector of nucleic acid, particularly as a potential carcinogen in cervical cancer. However, research indicated that the sperm head is a vector of arginine-rich histones which acts superficially at the surface of the target cell and only quite early during the first moments of contact.

- 0993 DO HUMAN TUMORS SHOW A CHROMOSOME PATTERN SPECIFIC FOR EACH ETIOLOGIC AGENT. (E.) Rowley, J. D. (Pritzker Sch. Med., U. Chicago, Ill.). *J Nat'l Cancer Inst* 52(2):315-320, 1974.

It is hypothesized that: the chromosome pattern within affected tumor cells may be consistent for a disease produced by a single etiologic agent; the chromosome pattern may be highly variable for a given disease that can be produced by different etiologic agents; within a disease category, it may be possible to distinguish individuals whose affected cells have the same chromosome abnormality and thus to identify those whose disease may be due to the same etiologic agent; and a single

etiologic agent may cause the same chromosome abnormality in cells from each individual, this probably being less valid for a genetically heterogeneous population. Human diseases which show a consistent chromosome pattern are chronic myelogenous leukemia, meningioma, and Burkitt's lymphoma. On the other hand, acute myelogenous leukemia, polycythemia vera, and myelodysplasia show apparently variable chromosome patterns; no specific etiologic agent has yet been identified for any of these diseases. In animals, genetic factors, which segregate in a Mendelian fashion and can be located on a specific mouse chromosome, control the susceptibility or resistance of a particular inbred mouse strain to infection with murine leukemia virus. In a susceptible strain of rat or Chinese hamster, the particular chromosome abnormality observed depends on the mutagenic agent used in the experiment. Histologically similar tumors caused by different agents have different karyotypic patterns.

- 0994 A STUDY OF LYMPHOCYTIC β -GLUCURONIDASE IN VARIOUS BENIGN AND MALIGNANT LYMPHATIC PROCESSES. (E.) Woessner, S. (Fac. Med., U. Barcelona, Spain), F. Milla and C. Rozman. *Acta Haematol* 51(2):84-90, 1974.

Lorbacher's technique was used to study the β -glucuronidase activity in the blood of 50 normal controls and 101 patients with benign or malignant lymphatic processes. An average of 44% of the lymphocytes of the controls were positive for β -glucuronidase. There was a significant decrease in the activity of β -glucuronidase (mean 5.7%) in the patients with chronic lymphocytic leukemia and in half of the patients with infectious mononucleosis. The β -glucuronidase values did not differ from normal in acute lymphoblastic leukemia, and were within or above normal limits in Hodgkin's disease and non-Hodgkin lymphomas. The study of lymphocytic β -glucuronidase can provide useful information in the diagnosis of both peripheral and central lymphocytoses.

- 0995 ABO BLOOD GROUPS AND CANCER. (E.) Newell, G. R. (Nat'l. Cancer Inst., Bethesda, Md.), J. E. Gordon, A. P. Monlezun and J. S. Horwitz. *J Nat'l Cancer Inst* 52(5):1425-1430, 1974.

Diagnostically confirmed cases of cancer of the breast, cervix, pancreas, colon, stomach, and leukemia were obtained from the Charity Hospital of Louisiana Tumor Registry, and their ABO blood group distribution was compared with that of 5000 individuals who voluntarily donated blood to the same hospital. For the comparison group, there were no differences in ABO distribution between the sexes, whereas blacks had a greater frequency of type B and a lesser frequency of type A than whites. There was no excess risk for cancer of the breast, cervix, or colon in blood group A, but a 50% excess risk for cancer of the pancreas among black males and white females. For stomach cancer, risk among white females increased twofold and risk among blacks increased 30-60%. For leukemia, the relative risk in blood group A was 1.74 among black males and 2 among white females. Although

none of these increases in risk are statistically significant, they are within the range of higher risk for pancreatic and stomach cancer reported in other studies. The association between blood group A and leukemia could be a chance occurrence.

- 0996 RELATIONSHIP BETWEEN HYDRATION AND PROTON NUCLEAR MAGNETIC RESONANCE RELAXATION TIMES IN TISSUES OF TUMOR-BEARING AND NON-TUMOR-BEARING MICE: IMPLICATIONS FOR CANCER DETECTION. (E.) Hazlewood, C. F. (Baylor Coll. Med., Houston, Tex.), G. Cleveland and D. Medina. *J Nat'l Cancer Inst* 52(6):1849-1853, 1974.

Hyperplastic alveolar nodule outgrowth lines with mammary tumor-producing capability were transplanted into the inguinal mammary gland-free fat pads of syngeneic 3-wk-old BALB/c females. Mammary tumors from C3H and C3Hf mice were transplanted s.c. into 4-month-old syngeneic females near the right axilla. Preneoplastic mammary nodule tissue and mammary neoplasms could be distinguished from normal murine pregnant mammary tissue by nuclear magnetic resonance (NMR) relaxation times (T_1 and T_2) and diffusion coefficient of water protons. The presence of a growing mammary tumor in the host altered the T_1 and T_2 of water protons in other organs such as spleen and kidneys. These changes in T_1 and T_2 were independent of changes in organ hydration. The presence of an oncogenic mammary tumor virus in C3H mice also significantly influenced the T_1 and T_2 of water protons in some organs. These data strongly suggest that the water-macromolecular interactions in tissues are altered by several different factors (i.e., the presence of a tumor or virus in the host) and are not strictly correlated with tissue hydration. The data suggest that NMR spectroscopy may be useful in cancer research and cancer detection.

- 0997 CONTROL OF CELL SURFACE TOPOGRAPHY. (E.) Berlin, R. D. (Harvard Med. Sch., Boston, Mass.), J. M. Oliver, T. E. Ukena and H. H. Yin. *Nature* 247(5435):45-46, 1974.

According to the fluid mosaic model of membrane structure, surface proteins are free to diffuse in a lipid matrix and thus to assume a random or homogenous distribution over the cell surface. Cellular components which are sensitive to colchicine alkaloids can affect the topography of certain surface elements and the topographical heterogeneity of specific surface elements can be altered by colchicine. In some systems (e.g. virus transformed fibroblasts fixed with paraformaldehyde and lymphocytes), the movement of concanavallin A (con A) binding site clusters induced by con A occurs only after colchicine treatment, whereas the concentrative movements of transport carriers and lectin binding sites induced by phagocytosis do not occur after colchicine. It is hypothesized that, in all cases, colchicine abolishes the attachment of membrane proteins to mobile cellular structures, permitting their association by exogenous cross-linking agents on the one hand, but abolishing cell-directed movements on the others. With regard to the nature of these colchicine-sensitive

linking structures, their pharmacological specificity parallels that of microtubular proteins. Contractile structures, perhaps microfilaments, may interact with these colchicine-sensitive elements in order to facilitate movements of the surface proteins.

0998 TUMOR GRADING BY IMPLANTATION IN EMBRYOS.

II. GRADING OF SOME HUMAN ASTROCYTOMAS.

(E.) Sherbert, G. V. (U. Coll. Hosp. Med. Sch., London, England) and M. S. Lakshmi. *J Natl Cancer Inst* 52(3):687-692, 1974.

Six human astrocytomas were graded by a system based on assessment of cellular response of 16- to 18- hr chick embryos to implanted tumors. Such grading of astrocytomas did not correlate with the grading system of Kernohan *et al.* Although one grade 5 astrocytoma was histologically assessed as gliosis with small areas of low malignancy glioma, the second grade 5 tumor was given Kernohan Grade III. The remaining four astrocytomas were all Kernohan Grade IV but were graded in embryos as 8-12. Whereas the Kernohan grading of the astrocytomas did not correlate with the survival times of the patients, grading in embryos showed a positive correlation. The survival times decreased with increase of the product of grade in embryo X age of the patient. This grading system may allow prognosis assessments of individual cases.

0999 GENESIS OF THE Ph¹ CHROMOSOME. (E.) Whang-

Peng, J. (Natl. Cancer Inst., Bethesda,

Md.), E. C. Lee and T. A. Knutseh. *J Natl Cancer Inst* 52(4):1035-1036, 1974.

Five high-quality special Giemsa stain preparations were prepared from the bone marrow of patients with chronic myelogenous leukemia (CML). Two of the patients initially had a single Ph¹ chromosome and subsequently developed dicentric Ph¹ chromosomes; the remaining three patients all had 46 chromosomes, including the Ph¹ chromosome. All preparations had distinct 22q12 banding patterns. The deleted portion of the Ph¹ chromosome separated from the 22 chromosome at the 22q12 region and translocated onto the #9 chromosome at the 9q34 region. The extra material in chromosome #9 was not further lengthened if there were more than one Ph¹ chromosome involved. Grossly, the translocation appeared to be balanced, but there is no method available to rule out the involvement of mutation or missing genes.

1000 PROSTAGLANDIN E (PGE) CONTROL OF CELL PROLIFERATION IN VITRO: CHARACTERISTICS OF

HT-29. (E.) Thomas, D. R., (Washington U. Sch. Med., St. Louis, Mo.), G. W. Philpott and D. M. Jaffe. *J Surg Res* 16(5):463-465, 1974.

Dispersed cell cultures of the human adenocarcinoma line, HT-29 were studied. Under control conditions, HT-29 had a very rapid doubling time, averaging 1.5 hr. HT-29 synthesized small amounts of PGE, mean 0.13 ng/10⁶ cells/day. Dibutyryl cyclic AMP (1 mM) resulted in significant inhibition of cell proliferation, very pronounced in assays performed 4 days

after the start of the experiments. Simultaneously, PGE production was significantly stimulated, again very significantly so at the 4-day assay point. Indomethacin (10⁻⁸M) included in the media of HT-29 resulted in almost total inhibition of PGE synthesis, and a significant stimulation of cell proliferation. Culture of HT-29 in 3 μM PGE, resulted in significant suppression of cell proliferation, of -48%, -41%, -60%, and -72% at days 1, 2, 4, and 6, resp. These results indicate that a human adenocarcinoma tumor line responds as do other tumor lines to the inclusion of dibutyryl cyclic AMP, PGE₁ and indomethacin in the media. This cell line offers two advantages: first, HT-29 *in vitro* synthesizes carcinoembryonic antigen and, secondly, HT-29 can serve as a prototype for studying proliferation of other monolayer derivatives of human adenocarcinomas.

1001 TOXIN-INDUCED PROLIFERATIVE CHANGES IN HEMATOPOIETIC AND MESENCHYMAL CELLS. (Ger.)

Müller, U. S. (Med. Clin., U. Munster, Germany), G. Schmitt and W. H. Hauss. *Verh Dtsch Ges Inn Med* 78: 689-693, 1972.

The ³H-thymidine labeling index was determined in mononucleated round cells in blood smears and in the myocardium of male Wistar rats injected with staphylolysin (0.1 U i.p.) or streptolysin (4.0 U i.p.). When ³H-thymidine was injected 24 hr before administration of either staphylolysin or streptolysin, the labeling index of mononucleated round cells and that of the myocardium were significantly increased. No change occurred when ³H-thymidine was injected 1 hr before sacrifice in rats injected with staphylolysin, but a significant increase occurred in the cell labeling rate in the myocardium of rats injected with streptolysin. These findings indicate that the hematopoietic system takes part in localized proliferation reactions in the form of mononucleated round cells which are capable of undergoing transformation into connective tissue cells. It is postulated that these round cells originate in the thymus and lymphatic system.

1002 EFFECT OF ERYTHROPOIETIN ON HUMAN BONE MARROW CELLS IN VITRO. III. STUDIES OF

ACUTE LEUKEMIA. (E.) Chiyoda, S. (Third Dept. Internal Med., Fac. Med., U. Tokyo, Japan), H. Mizoguchi, S. Susuki, F. Takaku and V. Miura. *Proc Soc Exp Biol Med* 146(3):684-687, 1974.

Bone marrow cells from five untreated patients with acute myelogenous leukemia (AML), five untreated patients with acute lymphocytic leukemia (ALL), and five normal controls were cultured in the presence of exogenous erythropoietin (EP). EP (0.1 U/ml) increased the rate of heme synthesis in the control cells by 600%, the increase being linear with a log dose of EP up to 0.2 U/ml. In all cases, the response to EP in the AML cells was less than that in the control cells. In contrast, in the ALL cells, the response to EP was maintained at normal or even slightly higher levels. The results suggest that there may be a difference between the two types of leukemia with respect to the mode of involvement of the eryth-

roid cells. There appears to be a more specific suppressive mechanism affecting the erythroid cells in AML than in ALL.

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ABE, H.	ANDERSON, R.E.	BALINSKY, D.
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ABOIN, J.	ANDZHAPARIDZE, O.G.	BALTIMORE, D.
1059*	766	812
ADAMSON, R.H.	ANGHILERI, L.J.	BANERJEE, M.R.
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ADENIS, L.	ACKI, T.	BARRA, Y.
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AGHAI, E.	ARCHER, V.E.	BARTSCH, H.
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AKHTAR, M.	ATKIN, N.B.	BELL, L.
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AKIF'EV, A.P.	ATKINSON, G.W.	BELMAN, S.
624	709	653
AKIN, F.J.	ATKINSON, J.N.C.	BELPOMME, D.
681	967	921*
AKSOY, M.	AUERBACH, O.	BELSKY, J.L.
647	621	742
AL-SARRAF, M.	AUFDERHEIDE, A.C.	BELTZ, B.
876	1041*	1176*
ALBIN, R.J.	AUGENER, W.	BEN-SASSON, Z.
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ALBRECHT, C.F.	AUSTWICK, P.K.C.	BENNETT, D.G.
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DINCOL, K. 647	ESBER, C.E. 868	FOERSTER, W. 1054*
DINES, D.E. 1028*	ESCRIBA, A. 1059*	FOLEY, G.E. 1143*
DJALDETTI, M. 1022*	ESPINOS, D. 1059*	FOLKMAN, J. 990
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DONNER, L. 807	EVANS, N.J.R. 963*	FOUCHEY, D. 765
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GAZE, S.E. 1077*	GOSPODAROWICZ, D. 827*	HAAG, H.L. 1131*
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GERSTL, B. 1159*	GRAESSMANN, M. 863	HAKALA, T. 754
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GODAL, T. 925*	GREENBERG, M. 955	HANDLER, E.S. 1015*
GOH, K.-O. 1150*	GREENBLATT, M. 648	HANKINS, W.D. 815
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HANS, J.P.	HELWIG, E.B.	HOLOWIECKI, J.
1121*	1042*	1152*
HANSEN, E.R.	FENLE, G.	HOLT, P.S.
914*	768	872
HARD, G.C.	FENLE, W.	HONG, C.C.
669	768	901
HARDY, D.W., JR.	HENNEKEUSER, H.H.	HONG, J.G.E.
776	1139*	957
HARDY, J.	HENRY, J.I.	HOOD, C.
678	666	792
HARDY, W.D., JR.	HENRY, R.	HOOK, R.R., JR.
859	927*	1169*
HARLOZINSKA, A.	HEPYUEKSEL, T.	HORAI, T.
844	647	939*
HAROZ, R.K.	HERBERMAN, R.B.	HORIUCHI, S.
838*	779, 894	658
HARRIS, C.C.	HERBST, A.L.	HORMES, R.
636, 1021*	956	1048*
HARRIS, J.A.	HERBSTREIT, I.	HORN, S.W.
864	976	1035*
HARRIS, J.R.	HERING, F.	HORN, R.G.
953*	680	951*
HARRIS, L.F.	HERMETET, J.C.	HORNING, M.G.
931*	1061*	725*
HARRIS, M.	HEWETSON, J.	HORWITZ, A.F.
1179*	768	832*
HARRISON, M.	HEYDEN, G.	HORWITZ, J.S.
1032*	1123*	995
HARRISON, Y.E.	HICKEY, R.J.	HOWELL, S.B.
717*	720*	868
HARRY, D.S.	HICKIE, R.A.	HREN-VENCELJ, H.
667	1130*	752
HART, M.N.	HIESCHE, K.D.	HUANG, R.C.C.
1037*	747*	1144*
HARTMANN, D.	HIJMANS, W.	HUCHET, R.
886	1131*	921*
HASHIMOTO, K.	HILL, M.	HUEBNER, R.J.
941*	790	797
HASLAM, S.	HILLEMANN, M.R.	HUGGINS, C.B.
806	925*	642
HATANAKA, M.	HILLMAN, E.A.	HUGHES, J.H.
1004*	799	931*
HATTEN, M.E.	HIRAI, H.	HULU, V.
832*	903	1186*
HAUGHTON, G.	HIRAKI, K.	HUMEAU, C.
861	1094*	1067*
HAUSS, W.H.	HIRASHIMA, S.	HUNG, P.P.
1001	1024*	794
HAWKINS, H.C.	HIRAYAMA, C.	HURLIMANN, J.
657	919*	1158*
HAYES, C.	HIRT, B.	HURSEY, M.L.
1151*	831*	1034*
HAZLEWOOD, C.F.	HOBBS, B.A.	HUSTINX, T.W.J.
996	789	746*
HEBERLING, R.L.	HOBBS, J.R.	IBAYASHI, H.
761	1017*	919*
HEFNER, M.H.	HOCK, B.	IHLE, J.N.
1078*	881	890
HELMANN, R.	HOELZER, D.	IKAWA, Y.
774	1009*	755
HELLER, A.	HOENIG, M.	IKEDA, Y.
950*	676	658
HELLMAN, A.	HOFFMANN, H.	ILYIN, K.V.
761, 783, 816	863	781
HELMICH, C.	HOLDEN, H.T.	IMOTO, A.
806	779	658
HELMKE, R.J.	HOLLARD, D.	INABA, Y.
761, 783	1065*	941*

INCH, W.R.	JOHNSON, R.T.	KENNEY, F.T.
987	735	890
INGLIS, R.J.	JOLLY, R.D.	KERN, F.G.
1197*	1180*	1177*
IOCHIM, H.L.	JONES, D.J.	KESZTELE, V.
780	654	1060*
IONESCU, T.	JOSHI, V.V.	KEY, C.R.
753	686	740
IRIE, K.	JUNGMAN, R.A.	KEYSELL, G.R.
875	1008*	643
IRIE, R.F.	KABAT, E.A.	KHACHATURIAN, L.M.
875	909	849
IRINO, S.	KAISER, W.	KIEFER, G.
1094*	980	1108*
IRLIN, I.S.	KALCHEVA, V.	KIEFER, R.
781	962*	1108*
IRVINE, W.J.	KALTER, S.S.	KIEHN, D.
851	761, 783	804
ISACCHI, G.	KANEKO, A.	KILBUCK, J.H.
977	712	617
ITO, N.	KANI, T.	KILLMANN, S.-AA.
695	695	603
ITO, U.	KAPADIA, G.J.	KIM, N.
941*	713	848
IVANKOVIC, S.	KAPLAN, J.	KIMELBERG, H.K.
692	906	1142*
JACOBS, D.M.	KARL, H.J.	KIMMEL, G.L.
905	1193*	1086*
JACOBS, P.	KARPAS, A.	KIMURA, G.
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JAFFE, E.S.	KATSUTA, H.	KINSKY, R.G.
915*	662	845
JAKOBIEC, F.A.	KAUFMAN, D.G.	KIRCHNER, H.
1091*	636	779
JAMI, J.	KAUFMAN, J.J.	KIRK, J.
1149*	936	968
JANDER, H.P.	KAVERZNEVA, M.M.	KIRPICHNIKOVA, K.A.
856	1113*	1069*
JANDOVA, A.	KAWAMOTO, S.	KISH, V.M.
1114*	742	705
JANIEC, W.	KAY, S.	KISHIMOTO, H.
1152*	1043*	631
JAPA, J.	KAZANCHEVA, A.M.	KISS, I.S.
1152*	1053*	677
JARRETT, O.	KEAST, D.	KITAGAWA, M.
792	872	925*
JARRETT, W.	KEEHN, R.J.	KITHIER, K.
792	742	876
JEANTEUR, P.	KELLER, S.E.	KLEIN, E.
1012*	780	867
JENNER, P.	KELLERER, A.M.	KLEIN, G.
643	954	867, 902, 982
JENNINGS, S.R.	KELLERMANN, G.	KLEIN, H.
898	623	1055*
JEWKES, D.M.	KELLEY, S.P.	KLEIN, J.C.
984	799	743
JOBARD, P.	KELLY, H.	KLEPPING, C.
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1119*	805	770
JOHN, T.	KELLY, W.A.	KNAPP, W.
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JOHNSON, M.N.	KENDE, G.	KNECHT, M.E.
684	1186*	970
JOHNSON, R.E.	KENNEDY, A.R.	KNISPEN, R.R.
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| KNUTSEH, T.A.
999 | KUPCHIK, H.Z.
917* | LEBOWITZ, P.
805 |
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658 | KURIAKOSE, K.I.
1191* | LEE, E.C.
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659 | KURODA, Y.
731* | LEE, F.I.
667 |
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887 | KURRLE, E.
1009* | LEE, T.N.H.
805 |
| KODAMA, Y.
658 | KURTH, R.
925* | LEE, Y.C.
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| KOZACHENKO, M.A.
940* | LANGAN, T.A.
1197* | LEVINE, P.H.
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| KRANTZ, M.J.
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1161* | LIN, J.J.
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| KUMAR, V.
778 | LEAV, I.
1171* | LIN, J.-T.
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LORENZ, F. 1132*	MALUISH, A. 858	MCMAHON, J.M. 764
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MILLIS, A.J.T. 1102*	MUELLER, N. 863	NISHIE, K. 670
MILLS, J. 622	MUELLER, U.S. 1001	NOJI, N. 1156*
MILROY, W.C. 325	MUIR, D.C.F. 728*	NORDENSKJOLD, B. 1137*
MINASE, T. 712	MUNNEL, E.W. 612*	NOREED, W.P. 670
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MINNA, J.D. 795	MURPHY, G.P. 842	NOVIKOV, D.K. 911*
MISAKI, A. 1006*	MUSHINSKI, J.F. 973	NUGENT, F.W. 914*
MISDORP, W. 972	NADEL, E. 1107*	OBERTI, J. 1055*
MISHRA, L. 718*	NAGASAWA, H. 645	OBRECHT, P. 1139*
MISHRA, L.C. 716*	NAGAYO, T. 934	O'CONNOR, T.E. 786, 796
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O'HARA, J.R. 617	PARANJPE, M.S. 904	PERSAUD, V. 1179*
OIKAWA, A. 1110*	PARARAS, M. 947*	PERTSCHUK, L.P. 663
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OL'KHOVSKAIA, I.G. 1063*	PARKS, R.C. 1033*	PHILPOTT, G.W. 1000
OLSON, C. 925*	PARKS, W.P. 771	PIENTA, R.J. 810
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OWEN, R. 958	PAWLOWSKI, N.E. 654	POLO, M.I. 944*
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874	992	853
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637, 644	860	663
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975	985	870
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639, 713	813	1176*
PRASAD, K.N.	REUSCH, D.	ROSS, J.
1118*	1064*	755
PRICE, M.R.	REVEL, M.	ROSSATO, R.G.
953*	751	1154*
PRIGOGINA, E.L.	REVESZ, L.	ROSSI, M.H.
1113*	747*	954
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1021*	665	1157*
PRIORE, R.L.	RICH, M.A.	ROUGEON, F.
668	765	809
PRIVES, C.L.	RICH, R.	ROUSKAS, A.
751	765	738
PROCTER, B.G.	RICHARDSON, J.D.	ROWE, W.P.
723*	1098*	817
PROP, F.J.A.	RICHART, R.M.	ROWLEY, J.D.
988	1011*	993, 1134*
PRZYBYLSKI, C.E.	RICHIE, J.P.	ROYEN, P.M.
938	936	1027*
PYLEV, L.N.	RICHTER, A.	ROZENBLATT, S.
650	1034*	751
QASBA, P.K.	RICHTER, R.	ROZHKOVA, A.P.
758	844	1062*
QUAGLINO, D.	RICHTER, W.R.	ROZMAN, C.
605	942*	994
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1160*	980	1025*, 1026*
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1017*	1101*	615
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652	1149*	846
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1186*	890	748*
RANGAN, S.R.S.	ROBERTS, B.E.	RUTTEN, F.J.
798	751	746*
RAO, M.S.	ROBERTS, D.D.	RUZISCKA, P.
649	1199*	985
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889	1087*	835*, 838*
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1068*	1086*	1116*
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1168*	759	621
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639	803	843
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660	768	636
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814	700	1043*
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709	607	1140*
SPECK, B.	SUESS, R.	THAXTON, J.P.
1131*	635	880
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1084*	721*	1000
SPELSBERG, T.C.	SUGAYA, T.	THOMAS, W.R.
641	1047*	872
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688	847	1081*
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841	1136*	987
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774	1160*	740
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676	1002	899
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636	769	962*
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1119*	620, 649	853
SPRINGER, G.F.	SVOBODA, J.	TIMME, A.H.
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957	1084*	1154*
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937	773	760
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PREFACE

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
Ind.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	RNA	ribonucleic acid
i.m.	intramuscular	s.c.	subcutaneous
i.p.	intraperitoneal	sec	second(s)
IU	international unit(s)	U	unit(s)
i.v.	intravenous	UV	ultraviolet
kg	kilogram(s)	WBC	white blood cells (leukocytes), white blood count
LD ₅₀	median lethal dose(s)	wk	week(s)
m	meter(s)	wt	weight(s)
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		

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- 1201 CARCINOGENIC FACTORS IN THE ENVIRONMENT. (Ger.) Schmahl, D. (German Cancer Res. Ctr., Heidelberg). *Verh Dtsch Ges Inn Med* 78:25-34, 1972.

Because of differences in the incidence of various forms of cancer in different parts of the world and associations between these forms of cancer and environmental factors, many cancer researchers believe that about 90% of all human cancer is caused by exogenous chemical or physical factors. Chemical carcinogens may either be products of industry, such as polycyclic aromatic hydrocarbons and higher aromatic amines, or they may occur in nature as do aflatoxins and carcinogens of plant origin. Arsenic can also occur naturally in high concentrations in drinking water. The cancer morbidity and mortality is very high in some regions of Argentina and China where arsenic has been implicated. A number of drugs have also been implicated as carcinogens and should not be used unless there is some vital indication for them. Because of their carcinogenic potential, alkylating agents should not be used to treat immune diseases, but they may be life-saving when used to treat tumors. In some cases it is difficult to extrapolate the results of animal testing to man. Although isoniazid has produced lymphomas and pulmonary adenomas and alveolar cell carcinomas in large percentages of mice, it does not do so in rats and hamsters and is probably not carcinogenic in man. It has been established clinically that diethylstilbestrol causes vaginal adenocarcinomas in the daughters of mothers who have been treated with this drug during pregnancy. Similarly, animal experiments have demonstrated that nitrosamides, urethane, procarbazine, and arsenic produce cancer in the offspring of mothers treated with them during pregnancy. When given to pregnant rats, two noncarcinogens, ethylurea and sodium nitrite, react to produce ethylnitrosourea which is a carcinogen. Within 10-26 months after birth, the offspring develop tumors of the nervous system. Research is needed to provide more information on the distribution and action mechanisms of carcinogens. (29 references)

- 1202 TESTING FOR CARCINOGENS AND MUTAGENS. (E.) Magee, P. N. (No affiliation). *Nature* 249(5460):795-796, 1974.

While a number of exceedingly rare human tumors have been found to be caused by environmental chemicals, reliable tests for carcinogenicity and mutagenicity of environmental chemicals must be developed before the effects of environmental chemicals on the more common human tumors can be determined. A variety of such tests, based on long-term assessment in laboratory animals, now exist, but most of these tests are difficult, time consuming, and/or expensive. Based on the conclusion that demonstration of mutagenic activity in a chemical should give warning of its possible carcinogenicity, *in vitro* systems for measuring mutagenicity have been developed. Using a procedure whereby a spot-mitochondrial liver homogenate is incorporated into the agar plate used for the culture of test microorganisms, several chemical carcinogens, mainly planar aromatic compounds,

were shown to be frame-shift mutagens. This method has been extended to enable the detection of mutagens in urine. Mutagenically active metabolites were found in the urine of rats treated with the carcinogen 2-acetylaminofluorene, the activity of which was increased after treatment with β -glucuronidase. The urine of p-dimethylaminoazobenzene-treated rats also contained mutagenic components which were active only after treatment with β -glucuronidase and taka-diastase. The test system for urinary mutagens could readily be included in toxicity studies on laboratory animals and could be used to screen the urine of human populations for the presence of conjugated and unconjugated mutagens. (No references)

- 1203 THE ETIOLOGY OF CANCER OF THE BLADDER. (E.) Oyasu, R. (Northwestern U. Med. Sch., Chicago, Ill.) and M. L. Hopp. *Surg Gynecol Obstet* 138(1): 97-108, 1974.

Numerous agents have been suggested as urinary bladder carcinogens. Epidemiologic studies indicate that workers in the dye, textile, printing, rubber and cable, and plastic industries have an increased risk of developing bladder cancer. These industries use four compounds which have been shown beyond doubt to be bladder carcinogens in man: beta-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, and 4,4'-diaminobiphenyl. The following agents are strongly suspected of being of etiologic significance in the development of bladder cancer by the general population: dietary additives, schistosomiasis, abnormal tryptophan metabolism, tobacco smoking, and viruses. Various animal species have been used as experimental models for the study of induction of cancer of the bladder, and substantial progress has been made in the search for bladder carcinogens, etiologic factors, and the pathogenesis of this disease. Although knowledge of the tumorigenesis of the cancer remains limited and fragmentary, it appears certain that multiple agents are responsible for the induction of bladder tumors. Clinicians should watch carefully for continual exposure to possible carcinogens in what appear to be harmless procedures. Cooperative work by oncologists, ecologists, toxicologists, physicians, and those in public health service is urgently needed in the study of urinary bladder tumorigenesis. (128 references)

- 1204 VINYL CHLORIDE, P.V.C., AND CANCER. (E.) Anonymous. *Lancet* (7870):1323-1324, 1974.

To date, 19 workers throughout the world have reportedly developed angiosarcoma of the liver following a history of intermittently heavy exposure to vinyl chloride (VC) over periods of 12-27 years in polyvinyl chloride (PVC) manufacturing plants. Experimental work indicating a relationship between VC and cancer has heretofore gone unheeded because the experimental exposure levels were very high in comparison to those to which PVC workers are exposed and because experimentalists have often warned of hazards where no adequate evidence of real hazard exists.

There is no indication that PVC is itself dangerous or that it depolymerizes to produce VC. Unreacted VC which is present in newly manufactured PVC may, however, be released during storage and when the material is heated during the manufacture of PVC products. There have been no cases of angiosarcoma of the liver among PVC processors. In Great Britain, the current upper limit for exposure to VC in PVC manufacturing plant is 50 ppm with a maximum time-weighted average exposure of 25 ppm. In light of evidence that rats develop angiosarcoma of the liver following exposure to 50 ppm VC, these limits may be lowered. More systematic evaluation of industrially used chemicals is needed to determine the carcinogenic risks to workers. (No references)

- 1205 FIBER CARCINOGENESIS: IS ASBESTOS THE ONLY HAZARD? (E.) Stanton, M. F. (Nat'l. Cancer Inst., Bethesda, Md.). *J Nat'l Cancer Inst* 52(3):633-634, 1974.

Asbestos causes cancer when it separates into fibers with exceptionally small diameters that retain substantial lengths. In support of this hypothesis, fine, long fibers of durable materials completely unrelated to asbestos (glass and aluminum oxide) are similarly carcinogenic in the pleura of the rat, while nonfibrous particles of asbestos, glass, and aluminum oxide, as well as exceptionally short fibers of these materials, are far less carcinogenic. Thus, any type of durable fiber falling into the range of long, fine fibers may be carcinogenic. While minute fibers are abundant in our environment, most of the fibrous materials to which we are most commonly exposed consist largely of particles too large or too small to be considered potential carcinogens. The most hazardous fibers may be those of exceptional length with diameters in excess of 0.5 microns. The ultimate risk of fibers is a complex problem in that fibers can be subtle carcinogens which deviate from simple dose-response relationships and require long latent periods before showing carcinogenic activity. A relatively rapid way of determining the hazards of fibers would involve equating the number and size distribution of fibers in human tissue to cancer in man. Further information is also needed on the intimate events between cells and fibers which lead to cancer. Vigilance in detecting the presence of potentially carcinogenic fibers in the environment and in human tissues would prove profitable. (4 references)

- 1206 CHEMICAL DOSIMETRY IN SOMATIC CELLS AND ITS UTILITY TO MUTAGENESIS. (E.) Patterson, J. B. (Nat'l. Inst. Environmental Hlth. Sci., Research Triangle Pk., N.C.). *Environ Health Perspect* (6):195-199, 1973.

The relationship between the number of mutagenic events induced and the number of insults visited upon specific cellular macromolecules by chemical compounds is a central one in the study of chemical mutagenesis. Such studies require that the DNA be

isolated, degraded, and chromatographed. The DNA has generally been degraded by some form of acid hydrolysis, but controlled enzymatic hydrolysis methods have recently been introduced. A number of chromatographic separation techniques are available, combinations of which should allow detection of most of the altered bases as they exist in the cell. The chromatographed products are usually detected and identified by their UV absorption properties in the 210-350 nm range. Combinations of these various methods have been used to produce, isolate, and identify those altered bases which may be directly responsible for the initiation of a carcinogenic event. For example, regarding the interactions of alkylating agents with DNA, the major products of DNA alkylation are generally 7-alkylguanine, 3-alkyladenine, and 7-alkyladenine. The distribution of the minor methylation products, which include O-6-methylguanine, 1-methyladenine, and 3-methylcytosine, differs significantly among the different alkylating agents. There is some evidence that the alkylation of the O-6 of guanine in DNA could be related to the high mutagenic efficiency of S_N1 type alkylating agents, while the presence of 3-methylguanine residues in DNA treated with methyl methanesulfonate and dimethyl sulfate might provide the answer for the mutagenicity of the S_N2 alkylating agents. (32 references)

- 1207 TRAUMA AND ONCOGENESIS. (E.) Monkman, G. R. (Mayo Grad. Sch. Med., U. Minnesota, Rochester), G. Orwoll and J. C. Ivins. *Mayo Clin Proc* 49(3):157-163, 1974.

The literature concerning trauma and cancer is reviewed and discussed in the light of two illustrative cases. Certain types of trauma, including that from carcinogenic chemicals and ionizing irradiation, appear to be related to the development of malignancies. However, there is no evidence that single, uncomplicated trauma causes cancer. The award of compensation solely on the basis of the appearance of tumor after a single trauma is unjustifiable. Trauma may act as a cocarcinogen, especially in cancers of the skin, and there is adequate evidence suggesting that the metastatic spread of malignant tumors can be affected by trauma. Strict adherence to generally accepted criteria in medicolegal and compensation proceedings should result in fewer unjustified awards. (40 references)

- 1208 REVERSE TRANSCRIPTASE IN LEUKEMIC CELLS. (Ger.) Rainer, H. (Inst. Med. Clin., U. Vienna, Austria), P. Hocker, E. Pittermann and K. Moser. *Wien Klin Wochenschr* 86(5):117-122, 1974.

A reverse transcriptase, similar to the DNA polymerase found in oncogenic RNA tumor viruses, and different from major DNA polymerases of normal proliferating white blood cells has been isolated from leukemic cells and from the serum and leukocytes of a patient with pancytopenia who later developed acute leukemia. This suggests that detection of reverse transcriptase might be used to diagnose preleukemic

(1209-1211)

conditions. Properties of the purified enzyme include RNA sensitivity of the template and DNA sensitivity of the end product. Cross reactions have been obtained between reverse transcriptase from leukemic cells and the enzyme isolated from murine and primate RNA tumor viruses. It has been hypothesized that the reverse transcriptase in leukemic cells transmits genetic information from RNA to DNA in such a way that the oncogenic virus can be firmly fixed in the genome of eukaryotic cells. It is further suggested that new units of oncogenic virus can be produced subsequent to reverse transcription and that a normal cell is then transformed by the virus into a malignant one. Thus, once genetic information is anchored in host DNA, reverse transcriptase is no longer necessary for oncogenesis to proceed. It has been demonstrated experimentally that malignant transformation of rat kidney cells and infection with murine sarcoma virus can be prevented by pretreatment with inhibitors of reverse transcriptase such as cyclic rifampicin derivatives. These inhibitors have also proven selectively toxic to leukemic cells *in vitro*. (84 references)

1209 LYMPHORETICULAR NEOPLASIA IN IMMUNOSUPPRESSION: FACTS AND FANCIES. (E.) Kruger, G. R. F. (Path. Inst., U. Koln, Germany). *Beitr Pathol Bd* 151(3):221-223, 1974.

Data suggesting a causal relationship between a prolonged defective immunologic responsiveness and the development of lymphoreticular malignancies are reviewed. The types of immune deficiency states in man which are associated with an increased incidence of lymphoreticular neoplasia are: Swiss-type agammaglobulinemia, Wiskott-Aldrich syndrome, the Louis-Barr syndrome, IgA-deficient sprue, acquired dys- or agammaglobulinemia, and autoimmune disorders. Experimental manipulations in laboratory animals, including intentional and unintentional immunosuppressive measures, have also resulted in the development of lymphoma. Various hypotheses have been put forth to explain the pathogenesis of lymphoreticular malignancies. Tumorigenesis in immuno-suppressed individuals may result from interference with the physiological mechanism of immune surveillance and the subsequent development of a state of tolerance towards the tumor. Defective cellular immune reactivity may allow B-type lymphoid cells and atypical lymphoreticular cells to proliferate uncontrolled. A (virus)-transformed T-lymphocyte may initiate a chronic graft-versus-host reaction (GVHR) of normal T-cells against the abnormal ones; during the course of the disease, abnormal cells selectively proliferate. In addition to immunosuppression, a probably genetically determined hyperproliferation of the lymphoreticular system or the activation of leukemogenic viruses may lead to lymphoma development. A virus-related gene (the oncogene) may exist which is vertically transmitted and represents an inherited code for malignant transformation. Finally, a lack of response of functionally ineffective lymphoreticular cells to excessive antigenic stimulation may cause proliferation of stem cells to cope with the stimulus. (29 references)

1210 CANCER IMMUNOLOGY: BASIC EXPERIMENTS AND CLINICAL ADVANCES. (Ger.) Pasternak, G. (Ctr. Inst. Cancer Res., Berlin-Buch, Germany). *Arch Geschwulstforsch* 42(4):345-357, 1973.

The role of tumor-specific transplantation antigens (TSTA) in malignant transformation and tumor growth is not clear. If their production causes cell proliferation and invasion of tumor cells into surrounding tissue, it should follow that antigen-containing cells would be recognized as foreign by the host and be rejected. However, this does not happen in practice. Some tumor antigens are not specific and their presence in the cell does not induce transformation, while no TSTA have been detected in other tumors. Antigens induced by leukemia viruses have been found in thymus cells of all mouse strains, no matter whether the strain has a high or low incidence of spontaneous leukemia. Similarly, a leukemia virus antigen has been found in embryonic tissues of mouse strains that do not develop spontaneous leukemia, indicating that the strain must carry the gene for leukemia virus. These findings and others led to formulation of the oncogene theory, according to which neoplastic changes result from breakdown of regulation of RNA tumor virus operator gene by the host and indirect activation of the RNA virus oncogene. The breakdown in regulation can result from natural aging processes, genetic defects, endogenous hormonal or immunological aberrations, or exogenous carcinomas. Although the oncogene theory is supported by experimental findings, these findings do not explain the function of virus-coded antigens in normal cells. The application of immunological methods to the diagnosis and treatment of cancer is discussed. (24 references)

1211 RECENT IMMUNOLOGICAL FINDINGS IN HODGKIN'S DISEASE. (E.) Grifoni, V. (Inst. Clin. Med., U. Cagliari, Italy). *Tumori* 59(5):363-374, 1973.

Passive hemagglutination, cytotoxicity testing, and immunofluorescence were used to detect antilymph node antibodies in serum samples and lymph node sections from 73 Hodgkin's disease (HG) patients. In the passive hemagglutination test, 14 of 15 sera were positive for autoantibodies, and 62 of 73 sera were positive for alloantibodies; the titer ranged from 20 to 640 for both. In addition, the HG sera generally reacted against both auto and a series of allo-HG lymph node antigens, and the HG sera sometimes reacted against non-HG allo-lymphoid antigens. Serum antibodies could be absorbed by the lymph node antigen and some cross-reactions were observed. Serum antibodies could also be precipitated by the antigen and recovered by elution from the antigen-antibody complex; they proved to be IgG by immunodiffusion. Autoimmunofluorescence gave positive results on 14 of 15 patients. Direct immunofluorescence using autolymph node sections usually gave the following pattern: only a few cells showed fluorescence, the fluorescent cells were round and lymphoid in appearance, and giant cells were not affected by fluorescent antibodies. Cytotoxic antibodies active against autochthonous lymphocytes

were detected in the sera of 26 to 38 patients. The lymphocytes appeared to have been antibody-coated *in vivo*. Cytotoxic sera were also active against allogeneic lymphocytes from normal subjects, the cytotoxic activity being bound mainly to the gamma-globulin fraction. The data indicate that in Hodgkin's disease, normal immunological functions are defective and abnormal immunological mechanisms are in operation. (17 references)

- 1212 IMMUNE REACTIONS TO CANCER ANTIGENS. (Ger.) Oettgen, H. F. (Sloan-Kettering Inst. Cancer Res., New York, N.Y.). *Verh Dtsch Ges Inn Med* 78:751-755, 1972.

High titers of antibodies to Epstein-Barr virus (EBV) have been found in sera from many children with Burkitt's lymphoma, as have surface antigens for EBV and precipitating antibodies to soluble extracts of Burkitt's lymphoma cells. Antibodies against EBV have also been detected in subjects who have had infectious mononucleosis and in a large percentage of patients with squamous cell carcinoma of the nasopharynx. Several theories have been advanced to explain why EBV can produce an infectious disease in some subjects and cancer in others. It has been suggested that malaria may be a cofactor in the induction of Burkitt's lymphoma. It is also possible that different subtypes of *Herpes* viruses produce different diseases. A third possibility is that EBV is normally present in lymphatic tissue and that proliferation of this tissue results in increased virus production and therefore in increased antibody production. However, it is difficult to reconcile this hypothesis with the finding that serum antibodies to EBV are found in Burkitt's lymphoma and nasopharyngeal carcinoma, but not in other lymphomas or carcinomas. The best reason for regarding EBV as an oncogenic virus is that herpesviruses induce neoplasms in frogs, chickens, and primates. Prospective studies are currently in progress in Africa to determine whether only children who are negative for EBV antibodies later develop Burkitt's lymphoma. This would be strong evidence for causal relationship between EBV and Burkitt's lymphoma. The possible use of immunological methods to treat cancer is considered. (No references)

- 1213 IMMUNE SURVEILLANCE REVISITED. (E.) Kripke, M. L. (Coll. Med., U. Utah, Salt Lake City) and T. Borsos. *J Natl Cancer Inst* 52(5): 1393-1395, 1974.

The theory of immune surveillance postulates that one function of the immune system is to eliminate or prevent the multiplication of nascent malignant cells. Experimental work on a possible relationship between oncogenesis and the immunologic status of the host has produced contradictory results. Evidence from clinical studies favoring immuno-surveillance is twofold: a high frequency of malignancy is observed in patients with various immune deficiency diseases; and an increased frequency of autochthonous malignancies occurs in immunosuppressed patients with kidney transplants. However, immunosuppression or

immunodeficiency is not the sole explanation for the increased risk of cancer in these patients. In addition to obstacles unique to certain experimental systems, two general limitations apply to all experimental studies of immune surveillance: the inability to detect and measure immune surveillance directly; and the inability to abrogate even the measurable immune responses without alteration of other physiologic or homeostatic mechanisms. Thus, it is impossible at present to design an experiment that will prove or disprove the existence of an immune surveillance mechanism. It is better to ask the simple question: which agents or procedures are likely to increase the probability of neoplastic disease? (30 references)

- 1214 THE ORIGIN AND DEVELOPMENT OF HUMAN TUMORS STUDIED WITH CELL MARKERS. (E.) Fialkow, P. J. (Dept. Med., U. Washington, Seattle). *New Engl J Med* 291(1):26-35, 1974.

Most neoplasms which have been studied appear to have clonal origin, and thus are compatible with somatic mutation theories of tumorigenesis. However, two hereditary tumors, neurofibroma and trichioepithelioma, along with one reported case of carcinoma of the colon and perhaps some invasive cancers of the cervix have multicellular origin. Thus, somatic mutation theories of oncogenesis are not valid for all neoplasms. Chronic leukemias, myelocytic and lymphocytic are clonal diseases, thus rejecting the thought that once a cell undergoes leukemic transformation, normal cells are recruited to form the neoplasm. Whether acute lymphoblastic leukemia is clonal is not known as yet, but current findings seem compatible with cell-recruitment theories. Burkitt lymphoma has a clonal origin. Thus, either the viral-induced oncogenic change for this malignant process is a rare event, or the target for the virus is a single cell, or else many cells are altered by the virus, but once a transformed clone slips through the surveillance systems, growth of other clones is inhibited. Genetic marker studies of tumorigenesis are currently limited to neoplasms that either synthesize immunoglobulin or arise in G-6-PD heterozygotes. The electrophoretic G-6-PD variants occur only in black subjects, but when other suitable X-linked markers are discovered, many more populations and tumors can be investigated which will eventually lead to more effective preventive and therapeutic measures. (14 references)

- 1215 PRECANCEROUS LESIONS OF THE UTERINE CERVIX IN PREGNANCY. (E.) Koss, L. G. (Montefiore Hosp. Med. Ctr., Albert Einstein Coll. Med., New York). *CA* 24(3):141-143, 1974.

Morphologic evidence indicates that carcinoma *in situ* begins in the form of inconspicuous cellular changes affecting the squamous epithelium adjacent to the endocervical columnar epithelium. Spontaneous regression may take place in about 30-40% of the earliest lesions, or the initial changes may progress to involve squamous epithelium in the va-

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ginal portion of the cervix or extend into the endocervical canal where the process will mimic the squamous metaplasia. A variety of known and unknown factors, including biopsies, trauma, and the use of certain antibiotics, may influence the course of the initial changes. Every patient with a precancerous lesion of the cervix should be the subject of surveillance for life. Contrary to earlier belief, the precancerous lesions of the uterine cervix observed during pregnancy behave similarly to those in nonpregnant women, and it is pregnancy which is incidental in women with precancerous lesions of the cervix. Following detection of precancerous states by Papanicolaou smear in the pregnant women, expert cytologic assessment combined with colposcopy will result in an accurate determination of the histologic type, size, and location of the lesion. Properly treated, most patients with precancerous lesions can carry their pregnancy to term without jeopardy to their lives. (13 references)

- 1216 REFLECTIONS ON BIOCHEMICAL ASPECTS OF HUMAN CANCER. *THE LUCY WORTHAM JAMES LECTURE.* (E.) Bodansky, O. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.). *Cancer* 33(2):364-370, 1974.

A general review of research into the biochemical aspects of human cancer indicates that certain areas of study have been fruitful, both from a diagnostic point of view and as a contribution to the understanding of human neoplastic processes. However, there have been other areas which appeared promising but which later faded away and lost their specificity for cancer as investigations proceeded. By way of illustration, several areas of biochemical research are discussed in detail: a general blood test for early cancer; enzyme procedures in cancer; the steroid discriminant in breast cancer; and the carcinoembryonic test in colon-rectal cancer. In general, some of the most common types of cancer have been studied little in terms of their biochemical and basic scientific parameters while rare and esoteric tumors have been the subjects of detailed investigation. When a new diagnostic or prognostic procedure is proposed which is presumably specific for cancer, it should be explored in severe non-neoplastic diseases by several different groups of investigators. In addition, in coordination with continued clinical study, the biochemical and other basic aspects of those human organs which are the sites of common human cancers should be studied more intensively. (34 references)

- 1217 PROSTAGLANDINS AND CANCER: AN UPDATE. (E.) Jaffe, B. M. (Washington U. Sch. Med., St. Louis, Mo.). *Prostaglandins* 6(6):453-461, 1974.

Available information relating to the relationship between prostaglandins and cancer is reviewed. Various studies have indicated that the diarrhea associated with medullary carcinoma of the thyroid is caused by synthesized and released PGE₂ and PGF₂. Other amine-peptide, secreting tumors have also been shown to secrete large quantities of prostaglandins,

increased PGE concentrations having been found in the plasma of most patients with carcinoid, pheochromocytoma, and neuroblastoma. The transplantable mouse fibrosarcoma, HSMD₁, causes bone resorption *in vitro*; the bone-resorbing substance secreted by HSMD₁ cells is PGE₂. Indomethacin, which inhibits PGE₂ synthesis, pronouncedly inhibits the bone resorbing activity. Rats with Walker carcinosarcomas have hypercalcemia and soft tissue and osteolytic bony metastases; indomethacin lowers the serum calcium concentrations to normal and decreases the incidence of the bony metastases. These animal models may have important clinical counterparts. Bioassay, radioimmunoassay, and mass spectroscopic data indicate that PGE is synthesized *in vivo* and *in vitro* by neoplastic cells. Furthermore, malignant cells contain more PGE than normal cells, the predominant prostaglandin is PGE₂, most of the PGE₂ synthesized in cell culture is released into the medium, and, *in vitro*, increasing the concentration of PGE either exogenously or endogenously results in the inhibition of cell proliferation rates. Although it has been suggested that the effects of PGE are mediated via the cyclic AMP-adenyl cyclase system, the exact role and mechanism of action of the prostaglandins is still largely speculative. (34 references)

- 1218 SYMPOSIUM ON BREAST CANCER. (E.) Borden, E. C. (Johns Hopkins U. Sch. Med., Baltimore, Md.), R. R. Baker and M. D. Abeloff. *John Hopkins Med J* 134(2):65-75, 1974.

Recent evidence suggests that human breast carcinoma is caused by an oncornavirus. Viral-like particles are observed in human milk and oncornavirus markers such as reverse transcriptase, homologous RNA sequences and poly A-rich RNA have been found in human milk and breast cancers. The late development of second primaries in the opposite breast may represent a "reinduction", analogous to that observed in acute leukemia. Immunology studies suggest that breast cancer cells may possess a common antigen to which many breast cancer patients have an IgG antibody. In addition to a common reactivity between patients with breast cancer, cross neutralization between the sera of patients with breast cancer and MMTV have been found. Transmission in man is probably verticle with human milk being a primary factor. The familial nature of human breast cancer was noted as early as 1866. The effect of castration on the growth of established human breast cancer was noted first in 1869. The effects of estrogens, pregnancy and oophorectomy on the progression of breast cancer have since been well established. Dietary studies have correlated the intake of sugar and fat with breast cancer incidence. It is suggested that mothers with breast cancer in first-degree maternal relatives or mothers whose husbands have first-degree relatives with a history of breast cancer should not breast feed. Current experimental antiviral chemotherapeutic compounds hold great promise but will not be in general clinical application for another decade. These compounds, interferon, streptovirin, rifamycins, and polynucleotides, all have a

degree of specificity for viral events without effect on normal cell-metabolism, but all are more effective when given prior to the initiation of infection. (73 references)

- 1219 BLADDER CARCINOGENESIS IN RATS AND MICE: POSSIBILITY OF ARTIFACTS. (E.) Clayson, D. B. (Eppley Inst. Res. Cancer, U. Nebraska Med. Ctr., Omaha). *J Natl Cancer Inst* 52(6):1685-1689, 1974.

Although urinary bladder calculi have not been shown to lead to bladder tumors in man, in rats and mice there is a correlation between bladder stones and bladder tumors. The surgical implantation of artificial stones into rat bladders with prepared pouches has indicated that the presence of urine is necessary for tumor induction and has suggested that the pellet has a cocarcinogenic effect. 4-Ethyl-sulfonylnaphthalene-1-sulfonamide (ENS) given acutely to mice leads to necrosis of the luminal layers of the urothelium and to stimulated DNA and RNA synthesis. Given subacutely, ENS causes the bladder epithelium to become hyperplastic, and given chronically, it leads to bladder tumor development. The digenetic trematode *Schistosomum haematobium* leads to beharziasis and can lead to cancer in the human bladder, whereas *Trichosomoides crassicauda*, the rat bladder threadworm, had not been demonstrated to do so in the rat bladder. A large, single dose of oxolamine leads to necrotic changes in the bladder epithelium in rats and dogs, but not in mice. Continuous application leads to bladder tumors. Unlike stones and bladder parasites, this agent appears to liberate alkylamines in the urine as a result of its metabolism. (53 references)

- 1220 BREAST CANCER RESEARCH: PROBLEMS AND PROGRESS. (E.) Marx, J. L. (No affiliation). *Science* 184(4142):1162-1165, 1974.

One of every 15 women will probably develop breast cancer. Efforts are underway to identify those women at greatest risk. The incidence of breast cancer is 5 to 6 times higher in North America and northern Europe than in most of Asia and Africa. Differences in genetic and environmental factors, including diet, are thought to be responsible. Like most other cancers, breast cancer is primarily a disease of old age and appears to run in families. Statistics indicate that breast cancer appears less often in women who have had their first full-term pregnancy before age 30. The female sex hormones are likely involved in the mechanism by which reproductive history influences susceptibility. Both early and late onset of menstruation are associated with an increased risk. Although studies as yet indicate no connection between the disease and oral contraception, these results are viewed with caution as oral contraceptives have been in widespread use for less than 10 years, whereas it takes 15 to 20 years for breast cancer to develop. Hormones of the adrenal and pituitary glands have also been implicated. Many investigators think a virus similar to the mouse mammary tumor virus is in-

involved. A virus with the characteristics of an oncovirus has been found replicating in a line of cultured cells derived from a patient with carcinoma of the breast. Preliminary evidence indicates the virus may be of human origin. Preventive measures such as the use of drugs to inhibit viral expression or the activity of reverse transcriptase are under investigation. Control of breast cancer currently involves early detection and successful treatment. Detection prior to metastases is essential. Screening of large numbers of apparently healthy women is a key to controlling the disease and improving the survival rate. Thermography is becoming a useful initial tool in the diagnosis of cancer. Once localized breast cancer is detected, the primary treatment is surgery sometimes accompanied by radiation therapy. Cancers too extensive to remove are treated with radiation or chemotherapy and the removal of one or more of the 3 glands, ovaries, adrenals, or pituitary, known to influence tumor growth. Chemotherapy has recently been used as an adjunct to the primary treatment even though the patient may be clinically free of disease. The presence of carcinoembryonic antigen, methylated guanoxine, or human chorionic gonadotropin in the blood or urine permit identification of patients with a high risk of recurrence. (No references)

- 1221 CANCER OF THE ENDOMETRIUM. (E.) Barber, H. R. K. (Lenox Hill Hosp., New York), B. Reisman, S. C. Sommers and E. A. Graber. *Tex Med* 70(7):41-56, 1974.

The five-year survival rate for endometrial carcinoma patients ranges from 55.9 to 62.2% in various reports, indicating that the concept of this as a relatively benign type of cancer should be reevaluated. Cancer of the endometrium is predominantly a disease of peri- or postmenopausal age groups, with over 75% of the cases occurring after age 50. Early diagnosis is essential and attempts to isolate the high-risk candidates are being made. Abnormal pituitary function may be a prime etiological factor. Obesity, nulliparity, reduced glucose tolerance, hypertension, hyperestrogenism, continuous uninterrupted estrogen stimulation, menses continuing beyond age 50, histories of dysfunctional uterine bleeding and of anovulation are frequently associated with endometrial cancers. These and other suggested parameters help identify clinically the high-risk patient. Screening methods employing cytology have been more elusive. The first symptom is abnormal vaginal bleeding. In the diagnosis of the condition, the combination of sampling from the vaginal pool, endocervix, and an endometrial aspiration will increase the reliability to greater than 90%. It is urged that a curettage (fractional) should be carried out in every postmenopausal patient with a bleeding problem. Stages 0 through IV for endometrial cancer are described and specific therapy is discussed for each stage, including indications and instructions for the use of radiation therapy. The use of available data on hormone receptors in clinical oncology would aid in spotting the high-risk patients, offer a more logical method of selecting monitoring therapy, and supply a method for selecting

and controlling the management of recurrent endometrial cancer. Much work has been done in the association between cancer of the endometrium and hormone stimulation. The group at high risk for extrauterine spread of endometrial cancer have involvement of the lower uterus or cervix, histologic grade 3 lesions, and myometrial invasion. In patients with extrauterine spread, treatment of surgery or irradiation should be employed beyond the uterus and include the pelvic nodes. (17 references)

1222 MALIGNANT LYMPHOMA IN GHANA - PART I: A REVIEW OF SURGICAL MATERIAL AT THE KORLEBU TEACHING HOSPITAL FROM 1966 TO 1971. (E.) Anim, J. T. (U. Ghana Med. Sch., Accra), E. C. Christian and W. N. Laing. *Ghana Med J* 12(2):176-183, 1973. (21 references)

1223 CHROMOSOME ANOMALIES IN CANCER CELLS. (Fr.) Cadotte, M. (Hotel-Dieu, Montreal, Canada). *Can J Med Tech* 36(3):221-225, 1974. (24 references)

1224 LEUKEMIA: MUCH IS KNOWN, BUT THE PICTURE IS STILL CONFUSED. (E.) Maugh II, T. H. (No affiliation). *Science* 185(4145):48-51, 1974. (No references)

1225 VIROLOGICAL ASPECTS OF HUMAN TUMOR DISEASES. (Ger.) zur Hausen, H. (Inst. Clin. Virol., U. Erlangen, Germany). *Fortschr Med* 91(30):1176-1180, 1973. (20 references)

1226 SIR ERNEST LAURENCE KENNAWAY, FRS, 1881-1958: CHEMICAL CAUSATION OF CANCER THEN AND TODAY. (E.) Haddow, A. (The Lodge, Pollards Wood, Chalfont St. Giles, Bucks, England). *Persp Biol Med* 17(4):543-588, 1974. (417 references)

1227 CYTOLOGY OF CLEAR-CELL ADENOCARCINOMA OF GENITAL TRACT IN YOUNG FEMALES: REVIEW OF 95 CASES FROM THE REGISTRY. (E.) Taft, P. D. (Harvard Med. Sch., Boston, Mass.), S. J. Robboy, A. L. Herbst and R. E. Scully. *Acta Cytol* 18(4):279-290, 1974. (20 references)

1228 MACROGLOBULINEMIA-MYELOMA DOUBLE GAMMOPATHY. A STUDY OF FOUR CASES AND A REVIEW OF THE LITERATURE. (E.) Pruzanski, W. (Immunoglobulin Diag. Res. Ctr., U. Toronto, Canada), B. Underdown, E. H. Silver and A. Katz. *Am J Med* 57(2):259-266, 1974. (43 references)

- 1229 DIETHYLNITROSAMINE-INDUCED CHROMOSOME CHANGES IN RAT LIVER CELLS. (E.) Hitachi, P. M. (Dept. Cytogenetics, Med. Res. Inst., Tokyo Med. Dental U., Japan), K. Yamada and S. Takayama. *J Natl Cancer Inst* 53(2):507-516, 1974.

Male Donryu rats (aged eight wk) were given *ad lib* access to drinking water containing 50 ppm diethylnitrosamine (DEN). Cytogenetic studies were performed on the livers of these animals 3-20 wk after the beginning of carcinogen treatment. The number of polyploid cells in the triploid and tetraploid ranges increased to 20% at 4-8 wk but decreased to 17% at 12 wk and to 9% at 20 wk; 10 of 194 karyotypes had chromosomal abnormalities. Liver tumors were studied 28-38 wk after treatment. In the eight DEN-induced hepatocellular carcinomas, the chromosomes of most cells were in the diploid range; they were also in the diploid range in three of the four adenomas. In one adenoma, 63.3% of the cells were in the tetraploid range. Cells with chromosome numbers other than 42 were characterized by monosomy and/or trisomy of many chromosomes and by structurally abnormal chromosomes. The percentage of cells with 42 chromosomes tended to decrease with increasing tumor size, a tendency which was reflected in the mitotic frequencies. The frequency of chromosomal changes such as breakages was not noticeably increased in the cells from the DEN-treated animals or in the tumor cells with chromosome numbers in the diploid range.

- 1230 CARCINOGENIC AND HEPATOTOXIC EFFECTS OF DIETHYLNITROSAMINE IN HEDGEHOGS. (E.) Graw, J. J. (German Cancer Res. Ctr., Heidelberg), H. Berg and D. Schmahl. *J Natl Cancer Inst* 53(2):589, 1974.

The carcinogenic effect of diethylnitrosamine (DENA) on the livers of hedgehogs was investigated in two series of experiments. In the first series, nine animals were given five s.c. injections/wk of 0.6 mg/kg DENA. After nine months, the dosage was increased to 6 mg/kg. All animals died within 13 months after the experiment began. In the second series, 13 animals were given five s.c. injections/wk of 6 mg/kg DENA in NaCl solution. All animals of this series died after three-eight months. Marked liver dystrophy was detected by gross dissection in all animals. Toxic injuries of the liver parenchyma, malignant hepatomas, and benign adenomas of the lung were observed. No pathologic changes were seen in untreated animals.

- 1231 PROLIFERATIVE RESPONSE IN THE RAT KIDNEY INDUCED BY A SINGLE, CARCINOGENIC DOSE OF DIMETHYLNITROSAMINE. (E.) Hard, G. C. (Baker Med. Res. Inst., Prahran, Victoria, Australia) and D. M. Shaw. *Cell Tissue Kinet* 7(5):433-441, 1974.

The pattern of DNA synthetic activity in the Wistar rat kidney was monitored with autoradiography during the three wk following a carcinogenic dose of dimethylnitrosamine (DMN, 60 mg/kg i.p.). Depending

on cell class and location, DNA synthesis was constantly depressed for the first one or two days throughout all zones of the kidney. Mesenchymal cells of the cortex and outer band of the outer medulla began a wave of stimulated activity at the third day with a peak of response at the sixth day. Epithelial cells of these same two zones were slower to respond, attaining a peak of DNA synthetic activity at the tenth day. By the start of the third wk, activity had returned to normal or near-normal levels. These observations are discussed in relation to the known morphological events which occur in the kidneys of DMN-treated rats prior to the development of neoplasia.

- 1232 THE CARCINOGENIC EFFECT OF 2-OXO-PROPYL-PROPYLNITROSAMINE IN SPRAGUE-DAWLEY RATS. (E.) Althoff, J. (Med. Coll., Hannover, W. Germany), J. Hilfrich, F. W. Kruger and B. Bertram. *Z Krebsforsch* 81(1):23-28, 1974.

2-Oxo-propyl-propylnitrosamine (2-OPPN) (0.2, 0.1, or 0.05 of the LD₅₀) was administered s.c. once weekly for life to 12-wk-old male and female Sprague-Dawley rats. The LD₅₀ for 2-OPPN was 424 mg/kg for both sexes. The average survival of the rats decreased with increasing doses of 2-OPPN. The animals in the highest dose group (85 mg) tolerated the treatment for 12 wk, after which they began to deteriorate; the animals in the lowest dose group (21 mg) began to deteriorate after 33 wk. Hemorrhagic ascites were observed 15-46 wk after the beginning of treatment, their latency being dose dependent. The livers of most animals were enlarged, yellowish-brown in color, and developed surface nodules beginning 13-33 wk after the beginning of treatment. Most of the tumors found in the liver were hepatocellular carcinomas, with hemorrhages and invasion of neoplastic cells in the vascular system being frequently observed. The carcinomas also invaded the omentum, mesentery, pancreas, and diaphragm in some cases. Metastases were found in the lungs and lymph nodes of some animals. Some animals developed sarcomas, hemangiosarcomas, and hepatomas, and tumors were sometimes also seen in the nasal cavity, brain, esophagus, adrenal gland, ovary, and uterus.

- 1233 PRIMARY NEOPLASMS IN DOG LIVER INDUCED BY DIETHYLNITROSAMINE. (E.) Hirao, K. (Nara Med. U., Japan), K. Matsumura, A. Imagawa, Y. Enomoto, Y. Hosogi, T. Kani, K. Fujikawa and N. Ito. *Cancer Res* 34(8):1870-1882, 1974.

Clinicopathologic, angiographic, and histologic studies were made on primary hepatic neoplasms of various types induced in male mongrel dogs by 50, 100, or 500 ppm diethylnitrosamine (DENA) in drinking water given *ad libitum* for more than 50 wk. Grossly, tumorous livers appeared finely granular, rubbery, and hard with yellow or gray tumors and areas of hemorrhage. Monthly analysis of blood samples showed that RBC count, hemoglobin, and hematocrit content of DENA fed dogs decreased while SGOT, SGPT, alkaline phosphatase and cholesterol levels

gradually increased. After DENA administration for 1 wk, selective angiography was able to demonstrate hepatic malignancies, hemangiomas, and hemangioendotheliomas prior to confirmation by postmortem examination. Histologic analysis of DENA-induced liver neoplasms showed 3 fibromas, 4 leiomyomas, 1 hemangioma, 10 hemangioendotheliomas, 4 fibrosarcomas, 1 leiomyosarcomas, 1 hepatocellular carcinoma, 1 cholangiosarcoma, and 1 undifferentiated cell carcinoma. Neoplastic areas of liver consistently showed proliferation of connective tissue, oval cell infiltration, and bile duct proliferation. Six of 14 dogs fed DENA developed squamous cell carcinomas of the nasal cavity.

34 SOME ASPECTS OF THE METABOLISM OF DIMETHYLNITROSAMINE IN THE RAT. (E.) Heading, B. (Brit. Ind. Biol. Assoc., Carshalton, Surrey, England), J. C. Phillips, B. G. Lake, S. D. Gangolli and A. G. Lloyd. *Biochem Soc Trans* 2(4):607-610, 1974.

The metabolism of ^{14}C -labeled dimethylnitrosamine (^{14}C -DMNA, 0.1-50 mg/kg) was studied in Wistar albino rats of both sexes following i.p., i.v., s.c. administration or by gastric intubation. Measurement of the amount of $^{14}\text{CO}_2$ respired for eight hr after administration of 5 mg/kg DMNA by each of the four routes showed loss of 57% of the administered dose. Studies with different DMNA concentrations showed that the rate of $^{14}\text{CO}_2$ excretion was dose dependent. Results from studies in which the rate of gastrointestinal absorption of ^{14}C -DMNA was measured showed that over 50% of the DMNA remained unabsorbed after 30 min in the ligated stomach but less than 5% remained after 30 min in the ligated small intestine. Rates of $^{14}\text{CO}_2$ excretion were determined following i.p. administration of ^{14}C -DMNA (5 mg/kg) to rats pretreated with unlabeled dimethylnitrosamine, phenobarbital, or 20-methylcholanthrene (MC). Although pretreatment with MC had no effect, pretreatment with DMNA and phenobarbital greatly increased metabolism of ^{14}C -DMNA up to twice the control value. DMNA pretreatment reduced liver microsomal cytochrome P450 content and activities of some of the mixed function-oxidases. Both phenobarbital and DMNA increased liver microsomal mixed-function-oxidase activity.

35 EFFECT OF BETA-OXIDIZED NITROSAMINES ON SYRIAN HAMSTERS. II. 2-OXOPROPYL-*n*-PROPYLNITROSAMINE. (E.) Pour, P. (Nebraska Med. Ctr., Omaha), J. Althoff, A. Cardesa, F. W. Krüger and U. Mohr. *J Natl Cancer Inst* 52(6):1869-1874, 1974.

2-Oxopropyl-*n*-propylnitrosamine (2-OPPN; 0.025, 0.05, and 0.1 of the LD_{50} given s.c. once weekly for life), a metabolite of di-*n*-propylnitrosamine (DPN) due to β -oxidation, was carcinogenic in the Syrian golden hamster. The main target organ of 2-OPPN was the respiratory tract, particularly the nasal cavity and the trachea. In the nasal cavity, malignant neoplasms were restricted to the posterior region; microscopically,

they were adenocarcinomas of various degrees of differentiation. In the trachea, the upper segment was the predilected site of tumor development (papillary polyps). A dose-response relationship could be established for tumor latency, but not for tumor incidence and multiplicity. In addition to the neoplasms in the respiratory system, numerous tumors were found in the liver (cholangiomas and hemangioendotheliomas) and kidneys (adenomatous cystic or tubular tumors). The biologic effect of 2-OPPN was compared with that of 2-hydroxypropyl-*n*-propylnitrosamine and methyl-*n*-propylnitrosamine, other metabolites of DPN by β -oxidation. Comparison at equitoxic doses gave no evidence that the metabolites are correlated with an increased carcinogenicity.

1236 REDUCTION BY PRETREATMENT WITH DIBENAMINE OF HEPATOTOXICITY INDUCED BY CARBON TETRACHLORIDE, THIOACETAMIDE OR DIMETHYLNITROSAMINE. (E.) Maling, H. M. (Natl. Heart Lung Inst., Bethesda, Md.), B. Highman, M. A. Williams, W. Saul, W. M. Butler, Jr. and B. B. Brodie. *Toxicol Appl Pharmacol* 27(2):380-394, 1974.

The effects of dibenamine pretreatment on the hepatotoxicity of carbon tetrachloride, thioacetamide, dimethylnitrosamine, allyl alcohol, and bromobenzene were studied. Pretreatment with dibenamine (25 mg/kg s.c. 48 and 24 hr prior to the administration of the hepatotoxic agent) protected Sprague-Dawley rats against the hepatotoxicity of CCl_4 , thioacetamide, and dimethylnitrosamine; it did not protect against the effects of allyl alcohol or bromobenzene. Protection was evidenced in terms of reduced plasma glutamic-pyruvic transaminase activity and reduced liver necrosis. In rats pretreated with dibenamine, the LD_{50} values for CCl_4 and thioacetamide were elevated, and liver triglycerides after CCl_4 and dimethylnitrosamine administration were reduced. Dibenamine protection against hepatotoxicity did not correlate with the degree of alpha-adrenergic receptor blockade. Pretreatment with three other alpha-adrenergic blocking agents (tolazoline, phenoxybenzamine, and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline) failed to protect rats against CCl_4 -induced hepatotoxicity. Dibenamine pretreatment did not protect male NIH-GP mice against elevations in plasma GPT induced by CCl_4 , nor did it reduce liver triglycerides in the mouse 24 hr after CCl_4 administration. Dibenamine did reduce the liver triglyceride concentrations measured 6 hr after CCl_4 . The effects of dibenamine are probably due to a blockade of the formation of active metabolites.

1237 CARCINOGENIC EFFECT OF N-NITROSAMINES RELATED TO BUTYL(4-HYDROXYBUTYL)NITROSAMINE IN ACI/N RATS, WITH SPECIAL REFERENCE TO INDUCTION OF URINARY BLADDER TUMORS. (E.) Okada, M. (Tokyo Biochem. Res. Inst., Japan) and Y. Hashimoto. *Gann* 65(1):13-19, 1974.

The carcinogenicity of four new N-nitrosamines related to butyl(4-hydroxybutyl)nitrosamine (BBN),

a potent and selective urinary bladder carcinogen, was investigated in male ACI/N rats. BBN (0.051%), butyl(2-hydroxyethyl)nitrosoamine (BHEN, 0.044%), butyl(3-hydroxypropyl)nitrosoamine (BHPN, 0.048%), propyl(4-hydroxybutyl)nitrosoamine (PHBN, 0.048%), and butyl-(2-oxopropyl)nitrosoamine (BOPN, 0.048%) were administered daily in the drinking water for 20-30 wk. PHBN, which has a 4-hydroxybutyl group like BBN, was a potent and selective urinary bladder carcinogen; however, its counterpart, BHPN, did not induce any tumors in any organs. BHEN induced hepatomas as well as papillomas in the esophagus. BOPN induced histopathological changes only in the liver and caused the development of hepatomas. Elevated serum glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, and alkaline phosphatase activities were observed following the administration of BHEN and BOPN.

1238 THE STRUCTURE OF METABOLITES OF THE CARCINOGEN, METHYL-*n*-BUTYLNITROSAMINE, IN RAT URINE. (Ger.) Blattmann, L. (German Cancer Res. Ctr., Heidelberg), N. Joswig and R. Preussmann. *Z Krebsforsch* 81(1):71-73, 1974.

A single dose of chromatographically pure methyl-*n*-butylnitrosamine (130 mg/kg) was administered p.o. to rats, 48-hr urine specimens were collected, adjusted to pH 5 and treated with a large excess of β -glucuronidase/arylsulfatase for several hr at room temperature. Free metabolites were extracted with dichloromethane which was evaporated under vacuum and replaced with dimethoxyethane. This solution was then reacted for several hr in a cold room with an ether solution of diazomethane to methylate acid groups. After filtration and evaporation of the solvent under vacuum, the residue was dissolved in CCl_4 and subjected to preparative thin-layer chromatography on silanized silica gel, using diisopropyl ether/ CCl_4 /isopropanol (3:6:1) as the mobile phase. After elution with CCl_4 or a mixture of methanol and CCl_4 (5:95) and filtration, the volume of the eluate was reduced and metabolites analyzed by gas chromatography and mass spectrometry. The metabolites were identified as: (1) methyl(4-hydroxybutyl)nitrosamine, (2) methyl(3-carboxypropyl)nitrosamine methyl ester, (3) methyl-(3-carboxy-2-hydroxypropyl)nitrosamine methyl ester, and (4) methyl(carboxymethyl)-nitrosamine methyl ester (or N-nitrososarcosine methyl ester). Thus, methyl-*n*-butylnitrosamine undergoes ω -oxidation to form alcohols and carboxylic acids or undergoes β -oxidation with shortening of the chain. The metabolites obtained must be tested for carcinogenicity to determine whether they are responsible for the organ-specific action of methyl-*n*-butylnitrosamine.

1239 BURCH ON SMOKING. (E.) James, J. R. (No affiliation). *New Scientist* 61(890):744-775, 1974.

The tar and nicotine contents of cigarettes vary greatly from one brand to another, as do the levels

of other smoke ingredients which could be implicated in lung cancer. Since the mechanism by which smoking produces lung disease is presently unknown, it should not be assumed that the mechanism is one of direct contact. If, for example, nicotine is a promoter of lung cancer, its mode of action could be indirect, via the blood stream. Once absorbed, it disarms the lungs defenses, possibly against carcinogens breathed in not only from tobacco smoke but sources such as diesel fumes or asbestos dust. The active agent might also be radioactive material from cigarette lighter flints. Professor Doll's theory is consistent with the idea that some people are, by hereditary endowment, more resistant to the carcinogenic effects of smoking than others.

1240 EFFECT OF AMINOACETONITRILE ON THE METABOLISM OF DIETHYLNITROSAMINE DURING LIVER CARCINOGENESIS. (E.) Mundt, D. (Middlesex Hosp. Med. Sch., London, England) and D. Hadjiolov. *J Natl Cancer Inst* 52(5):1515-1520, 1974.

The effect of chronic administration of aminoacetonitrile (AAN, 80 mg/kg s.c. 3 times/wk for 4 or 16 wk on the metabolism of ^{14}C -diethylnitrosamine (DEN) was measured as a function of the ethylation of liver RNA and $^{14}\text{CO}_2$ exhalation in Wistar rats continuously fed unlabeled carcinogen (4.8 mg/kg DEN 5 days/wk for 4 or 16 wk). The results were compared with those of acute experiments in which a single application of ^{14}C -DEN led to $^{14}\text{CO}_2$ exhalation and ethylation of liver RNA, whereas both effects were significantly lower after a single injection of AAN. After continuous feeding with DEN followed by a dose of ^{14}C -DEN, the exhalation of $^{14}\text{CO}_2$ was reduced in those rats which had also been continuously treated with AAN. In rats fed DEN continuously but given no further treatment, no inhibition in the output of $^{14}\text{CO}_2$ was recorded, compared with that of the acute experiment. However, the exhalation was prolonged. Chronic administration of AAN and DEN together also significantly decreased the ethylation rate of liver RNA in rats. The influence of AAN treatment during DEN carcinogenesis in rats was investigated in rats fed 1.4 mg/kg DEN 5 days/wk for 5 months. A change of organotropy with development of esophageal tumors was established; rats fed only DEN developed liver tumors. The possible function of carcinogen metabolism in induction of esophageal and liver tumors is discussed.

1241 RAPID FORMATION OF CARCINOGENIC N-NITROSAMINES BY INTERACTION OF NITRITE WITH FUNGICIDES DERIVED FROM DITHIOCARBAMIC ACID *IN VITRO* UNDER SIMULATED GASTRIC CONDITIONS AND *IN VIVO* IN THE RAT STOMACH. (E.) Eisenbrand, G. (Inst. Toxicol. Chemotherapy, German Cancer Res. Ctr., Heidelberg), O. Ungerer and R. Preussmann. *Food Cosmet Toxicol* 12(2):229-232, 1974.

The formation of the carcinogen dimethylnitrosamine (DMN) from the fungicide bis-(dimethyldithiocarbamate) zinc (ziram) in the presence of sodium nitrite was

studied *in vitro* under conditions similar to those existing in the stomach and *in vivo* in the male Wistar rat. Under these conditions, the optimum pH for the formation of DMN *in vitro* was 1.5-2.0; at pH 2.0, more than 1 mg DMN was produced after 10 minutes of incubation of 10^{-4} moles ziram with a twentyfold molar excess of nitrite. This corresponds to about 8% of the theoretical yield, assuming that two molecules of the carcinogen were formed from one molecule of ziram. Tris(dimethylthiocarbamato)iron (ferbam) and bis-(1-pyrrolidinylthiocarbonyl)-disulfide (DPTD) produced DMN and N-nitrosopyrrolidine, respectively, under the same conditions. After incubation for 15 minutes in the rat stomach with a 40-fold excess of nitrite, the average yield of DMN from 10^{-4} moles ziram was 126 μ g, corresponding to about 0.9% of the theoretical value. The individual values were 95 and 136 μ g in two fasted animals and 106 and 165 μ g in two nonfasted animals. Fungicides derived from dithiocarbamic acid are widely used in the production of fruits, leafy vegetables, and wine; residual levels of such fungicides in the human diet represent a potential starting material for the formation of carcinogenic nitrosamines when they are ingested with nitrite.

242 MALIGNANT TRANSFORMATION *IN VITRO* OF MOUSE FIBROBLASTS BY 7,12-DIMETHYLBENZ(a)ANTHRACENE AND 7-HYDROXYMETHYLBENZ(a)ANTHRACENE AND BY THEIR K-REGION DERIVATIVES. (E.) Marquardt, H. (Mem. Sloan Kettering Cancer Ctr., New York, N.Y.), J. E. Obergren, P. Sims and P. L. Grover. *Int J Cancer* 3(3):304-310, 1974.

K-region epoxides derived from 7,12-dimethylbenz(a)anthracene and from 7-hydroxymethylbenz(a)anthracene were tested for their ability to induce malignant transformation of the M2 clone of fibroblasts derived from C3H mouse prostate. The parent hydrocarbons, the corresponding K-region dihydrodiols and a phenol were also tested with these cells. The K-region epoxides induced transformation, but were somewhat less active than the hydrocarbons; the ring-hydroxylated derivatives were inactive. In other experiments, the addition of α -naphthoflavone inhibited the formation of water-soluble metabolites from, and the toxicity of, 7,12-dimethylbenz(a)anthracene without affecting malignant transformation. There may be several reasons for the comparatively lower transforming activity of compounds with the K-region epoxides of 7,12-dimethylbenz(a)anthracene, of 7-methylbenz(a)anthracene and of 7-hydroxymethylbenz(a)anthracene. The present results do not exclude the epoxides as proximate carcinogens in the case of 7-methylated benz(a)anthracenes. The effects of the proximate carcinogens certainly depend on the quantitative rates of formation, reactions and degradation. The lower activity may be due to a short intracellular half-life resulting partly from a higher rate of rearrangement to the phenol. Phenol formation could certainly contribute to epoxide toxicity. It is also possible that transformation may be cell-cycle dependent. A shorter intracellular epoxide half-life could result in unsynchronized cultures in fewer cells at the most sensitive stage of the cycle being exposed to the reactive intermediate.

1243 BIOTRANSFORMATION OF CARCINOGENIC DIALKYL-NITROSAMINES. ADDITIONAL URINARY METABOLITES OF DI-n-BUTYL- AND DI-n-PENTYLNITROSAMINE. (Ger.) Blattmann, L. (Max Planck Inst. Immunol., Freiburg, Germany) and R. Preussmann. *Z Krebsforsch* 81(1):75-78, 1974.

Urinary metabolites of dialkyl nitrosamines were analyzed in 48-hr urine specimens from a large number of BD rats after administration of a single dose of di-n-butyl nitrosamine (700 mg/kg) or di-n-pentyl nitrosamine (750 mg/kg) p.o. through a stomach tube. After hydrolysis of conjugated metabolites with glucuronidase/aryl sulfatase, metabolites were purified and concentrated by preparative thin-layer chromatography and gas chromatography. Metabolites with free carboxyl groups were methylated with diazomethane for analysis. Mass spectrometry of the products showed three new metabolites for di-n-butyl nitrosamine and one new metabolite for di-n-pentyl nitrosamine. These were identified as n-butyl(3-carboxy-2-hydroxypropyl) nitrosamine methyl ester, n-butyl(2-carboxyethyl) nitrosamine methyl ester, and n-butyl(carboxymethyl) nitrosamine as metabolites of di-n-butyl nitrosamine and n-pentyl(carboxymethyl) nitrosamine methyl ester as a metabolite of di-n-pentyl nitrosamine. These findings and previous reports in the literature suggest that dialkyl nitrosamines with longer alkyl chains are metabolized primarily by ω -hydroxylation and ω -oxidation. The resulting ω -carboxylic acids can then undergo β -oxidation of the carboxyl end which shortens the chain by 2 C atoms. While almost equal amounts of di-n-propyl nitrosamine appear to undergo ω -1-hydroxylation and ω -oxidation, ω -1-oxidation appears to play an unimportant role in the metabolism of dibutyl nitrosamine. Both metabolic pathways occur simultaneously or successively in the metabolism of di-n-pentyl nitrosamine.

1244 CHANGES IN ADRENOCORTICAL ACTIVITY DURING NITROSAMINE-INDUCED HEPATOCARCINOGENESIS. (Ger.) Hadjiolova, I. (German Cancer Res. Ctr., Heidelberg) and D. Hadjiolov. *Z Krebsforsch* 81(1):7-13, 1974.

Corticosterone contents of the adrenal cortex and plasma were measured in male Wistar rats during a 16-wk period when they were being given dimethylnitrosamine (1.4 or 4.8 mg/kg/day) or diethylnitrosamine (1.4 or 4.8 mg/kg/day) p.o. in their drinking water. After the first 4 wk of treatment, a slight increase was noted in both plasma and adrenal corticosterone levels. This is regarded as a manifestation of a nonspecific stress reaction. This slight increase in adrenal secretion is only transitory and does not cause hypertrophy of the adrenal cortex. Later the corticosterone levels decreased in the plasma and adrenal cortex so that they were significantly lower in animals given the larger doses of dimethyl- and diethylnitrosamine than in controls. At the same time, the lipid content of inner zones of the adrenal cortex increased, possibly because these steroid precursors could no longer be converted into corticosterone. Except for this functional change in sudanophilic substances, no pathological changes were observed in the adrenal cortex. Consequently, the de-

crease in adrenocortical activity cannot be attributed to direct action of nitrosamines. It is possible that this decrease in adrenocortical activity may result from liver damage, particularly if one bears in mind the important role the liver plays in steroid metabolism and in the protein binding of steroids. These findings did not establish any association between changes occurring in the adrenals and the development of liver cancer.

- 1245 NITROSATION OF PHENOLS IN SMOKED BACON. (E.) Knowles, M. D. (Food Sci. Div., Ministry Agr., Fisheries Food, Norwich, England.), J. Gilbert and D. J. McWeeny. *Nature* 249(5458): 672-673, 1974.

Samples of bacon were smoked by hanging them in a room filled with hardwood smoke or by spraying them electrostatically with liquid smoke. Such samples were examined in the raw and fried state and after simulated gastric digestion for nitroso and nitro-phenol compounds. Both smoking processes resulted in the deposition of phenols (mainly methylphenols, 4-substituted 2-methoxyphenols, and 4-substituted 2,6-dimethoxyphenols) in the meat matrix. No significant nitrogen-containing peaks were found in a sample of green bacon. Specifically, the spray-smoked bacon contained 6-nitro-*m*-cresol, 6-nitro-guaiacol, and 6-nitro-4-methylguaiacol, while the traditionally smoked samples contained 6-nitro-*m*-cresol (raw samples) and 6-nitro-*m*-cresol, 6-nitroso-4-methylguaiacol, 6-nitroso-4-propylguaiacol, and 6-nitro-4-methylguaiacol (fried samples). Thus, nitrate interaction with a wide variety of smoke phenols occurs in bacon during production, frying, and gastric digestion. The formation of nitroso- and nitro-phenols is sufficiently important for it to be taken into account during nitrite-balance studies in smoked meats.

- 1246 DURATION OF INHIBITION OF SYNTHESIS OF DNA IN TUMORS AND HOST TISSUES AFTER SINGLE DOSES OF NITROSOUREAS. (E.) Wheeler, G. P. (Biochem. Dept., South. Res. Inst., Birmingham, Ala.) and J. A. Alexander. *Cancer Res* 34(8):1957-1964, 1974.

The effects of three nitrosoureas, 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-(*trans*-4-methylcyclohexyl)-1-nitrosourea (MeCCNU), and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), were studied on *in vivo* DNA synthesis in various organs of plasmacytoma-bearing adult golden hamsters and male B6D2F hybrid mice bearing Lewis lung carcinoma. Animals received a single i.p. injection of BCNU (15 mg/kg), MeCCNU (36 or 40 mg/kg), or CCNU (57 mg/kg) and at various times thereafter were injected i.p. with ³H-methyl thymidine (³H-TdR). All animals were sacrificed two hr later and the acid-insoluble material was extracted from various organs. All results were compared to those from treated, nontumor-bearing animals. BCNU and MeCCNU caused a transient 90% reduction in ³H-TdR incorporation into acid insoluble fractions of liver, spleen,

lungs, kidneys, and brains of normal and tumor-bearing hamsters. The reduction of ³H-TdR incorporation into tumors was of greater magnitude and of longer duration. CCNU and MeCCNU produced a similar effect on ³H-TdR incorporation into lung and spleen of normal and tumor-bearing mice, but had little or no effect on ³H-TdR incorporation into liver, kidney, and brain. Inhibition of ³H-TdR incorporation by tumor in mice was also of greater magnitude and of longer duration than that of other tissues. It was concluded that BCNU, MeCCNU, and CCNU exert a relatively selective, damaging effect on tumor tissue in these systems.

- 1247 METABOLISM OF COMPLEX CARBOHYDRATES OF RABBIT SKIN DURING TREATMENT WITH 7,12-DIMETHYLBENZ(a)ANTHRACENE. (E.) Prodi, G. (Inst. Cancer, U. Bologna, Italy), A. M. Ferreri, P. Rocchi and S. Grilli. *Z Krebsforsch* 81(2):161-168, 1974.

7,12-Dimethylbenz(a)anthracene (DMBA, 0.3%) in acetone was painted on the shaved backs of adult male albino rabbits; the treatment was repeated twice weekly 1-10 times. Twenty-four hr after the last treatment, the animals were injected i.v. with glucosamine-1-¹⁴C (50 µC); they were killed 12, 48, 96, or 216 hrs after the injection. The levels of sialic acid-containing glycoproteins, hyaluronic acid (HA), and dermatan sulfate (CS-B) increased progressively during the first phases of DMBA treatment; the levels of the latter two mucopolysaccharides (MPS) decreased to control values or a little above with further treatments. The CS-B content of the treated areas decreased with the development of tumors, indicating that the level and variations in the metabolism of CS-B can be correlated with the early hyperplastic and later neoplastic changes which follow DMBA treatment.

- 1248 *IN VITRO* NEOPLASTIC TRANSFORMATION OF MOUSE SKIN CELLS: MORPHOLOGY AND ULTRASTRUCTURE OF CELLS AND TUMORS. (E.) Elias, P. M. (Natl. Cancer Inst., Bethesda, Md.), S. H. Yuspa, M. Gullino, D. L. Morgan, R. R. Bates and M. A. Lutzner. *J Invest Dermatol* 62(6):569-581, 1974.

Mixed cultures of epidermal and dermal cells from term fetuses of BALB/cAn mice were exposed to high concentrations (50 µg/ml) of 7,12-dimethylbenz(a)anthracene (DMBA) in medium containing Tween-80 or to medium with Tween-80 alone for 45 min. Within 5 wk, the cultures exposed to DMBA began to exhibit accelerated growth *in vitro* and an epithelioid morphology. These same changes occurred in the Tween-80-treated group starting around 15 wk in culture. Injections of cells into syngeneic hosts, beginning approximately 21 wk after treatment, gave rise to undifferentiated tumors. Animals receiving carcinogen-treated cells had more tumors than those receiving vehicle-treated cells. Whether this altered morphology in culture and malignant behavior *in vivo* was produced specifically by carcinogen and/or vehicle is yet to be determined.

- 1249 INHIBITION AND ENHANCEMENT OF MAMMARY TUMORIGENESIS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE IN THE FEMALE SPRAGUE-DAWLEY RAT. (E.) Feuer, G. (Dept. Clin. Biochem., U. Toronto, Canada) and J. A. Kellen. *Int J Clin Pharmacol* 9(1):62-69, 1974.

7,12-Dimethylbenz(a)anthracene (DMBA, dose not specified) was injected i.v. into female Sprague-Dawley rats on days 50, 53, and 56 of life. Within 150 days, 100% of the rats had developed tumors. Phenobarbital (0.02 mM/kg, i.p.), coumarin (1 mM/kg), and 4-methylcoumarin (1 mM/kg, by oral intubation) were administered to three additional groups of rats; the treatments were commenced 6 days before the first DMBA injection and continued for 15 days. Short exposure to coumarin, which inhibits drug hydroxylating liver enzymes, inhibited mammary tumor induction to the extent that only one tumor was found among 8 rats after 150 days. In contrast, 4-methylcoumarin and phenobarbital, both of which induce drug hydroxylating liver enzymes, did not inhibit tumor formation. The response was roughly proportional to the degree of enzyme induction caused by the latter two compounds. Thus, the metabolism of i.v. DMBA by a hydroxylase enzyme system bound to the hepatic endoplasmic reticulum is intrinsically associated with the carcinogenicity of this compound. The data obtained can be used in predicting the potential of a chemotherapeutic program against breast cancer.

- 1250 CHROMOSOME BANDING PATTERNS OF RAT FIBROSARCOMAS INDUCED *IN VITRO* BY TRANSFORMATION OF EMBRYO CELLS OR *IN VIVO* INJECTION OF RATS BY 7,12-DIMETHYLBENZ(A)ANTHRACENE. (E.) Olinici, C. D. (Nat'l. Cancer Inst., Bethesda, Md.) and J. A. DiPaolo. *J Natl Cancer Inst* 52(5):1627-1634, 1974.

The chromosomal constitution of three Sprague-Dawley rat cell lines transformed *in vitro* by 7,12-dimethylbenz(a)anthracene (DMBA, 1 µg/ml), two nontransformed lines isolated from DMBA-treated dishes, two untreated control cell lines, and five rat tumors induced *in vivo* by DMBA (1 mg s.c.) was investigated by the Giemsa banding technique. Rat embryo cells transformed by DMBA were isolated as early as the third passage. One line transformed *in vitro* and three tumors induced *in vivo* were mainly diploid, with a variable proportion of polyploid cells. The other two lines transformed *in vitro* and two of the tumors induced *in vivo* each showed particular numerical and/or structural chromosomal aberrations, preferentially involving chromosomes #1, 2, or 3. The same chromosomes were affected in the nontransformed and nontumorigenic lines isolated from DMBA-treated dishes. The untreated control lines showed only an accumulation of polyploid cells. Since neither a specific alteration of the chromosome distribution nor a particular and constant chromosomal aberration was found, it is concluded that *in vivo* or *in vitro* malignant transformation by DMBA leading to formation of fibrosarcomas is not directly caused by gross abnormalities of the chromosomes.

- 1251 ZINC INTAKE AND GROWTH OF A TRANSPLANTED HEPATOMA INDUCED BY 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE IN RATS. (E.) Duncan, J. R. (Dept. Biochem., U. Natal, Pietermaritzburg, South Africa), I. E. Dreosti and C. F. Albrecht. *J Natl Cancer Inst* 53(1):277-278, 1974.

The growth of an i.m. transplanted hepatoma induced by 3'-methyl-4-dimethylaminoazobenzene was significantly reduced in female Wistar rats maintained on diets low in zinc (0.4 µg/g) and high in zinc (above 500 µg/g), when compared with control animals given 60 µg zinc/g body wt. Greater inhibition of hepatoma growth was not achieved at toxic levels (2500 µg/g) of zinc intake. The viability of the transplanted tumor was not affected by the zinc intake of the animal at tissue implantation. It is possible that the general influence of zinc level on DNA synthesis accounts for the effects observed in transplanted tumor tissue.

- 1252 EFFECTS OF 7,12-DIMETHYLBENZ(A)ANTHRACENE AND ESTROGEN ON THE TRANSPLANTATION AND GROWTH OF A RAT PITUITARY TUMOR. (E.) Fang, V. S. (U. Chicago Pritzker Med. Sch., Ill.) and S. Refetoff. *Cancer Res* 34(1):225-229, 1974.

7,12-Dimethylbenz(a)anthracene, (20 mg p.o. through stomach tube or 10 mg i.p.) significantly enhanced the transplantability and stimulated the growth of a pituitary tumor in Wistar/Furth female rats. Estrogen (0.2 mg s.c.) was less effective than 7,12-dimethylbenz(a)anthracene. The combination of 7,12-dimethylbenz(a)anthracene and estrogen showed a synergistic effect. Hormone production by the tumor was not impaired by these treatments.

- 1253 AN 18-MONTH STUDY OF THE PARASITOLOGIC AND TUMORIGENIC EFFECTS OF HYCANTHONE IN *SCHISTOSOMA MANSONI*-INFECTED AND NONINFECTED MICE. (E.) Yarinsky, A. (Sterling Winthrop Res. Inst., Rensselaer, N.Y.), H. P. Drobeck, H. Freele, J. Wiland, and K. I. Gumaer. *Toxicol Appl Pharmacol* 27(1):169-182, 1974.

A study was undertaken to determine whether single i.m. injections of 12.5 and 50 mg/kg hycanthone (4 and 16 times the recommended human clinical dose) would induce or increase the development of neoplasms, specifically hepatomas, in normal Swiss Webster mice or in mice infected with *Schistosoma mansoni*. Fourteen different neoplasms were observed 43 times in 40 (10.3%) of 389 mice examined. The neoplasms were randomly distributed among the experimental groups. Hepatoma was diagnosed only once whereas lymphomas were observed in various organs of 13 mice and adenoma was observed in 12 mice. The data indicate that a single moderate or high dose of hycanthone does not increase the number of neoplasms, and also does not induce the development of hepatoma in either infected or noninfected mice. There was also no indication that infection with *Schistosoma mansoni* increased the incidence of neoplasms.

1254 PROLACTIN BINDING TO RAT MAMMARY TUMOR TISSUE. (E.) Kelly, P. A. (McGill U. Clin.,

Roy. Victoria Hosp., Montreal, Quebec, Canada), C. Bradley, R. P. C. Shiu, J. Meites and H. G. Friesen. *Proc Soc Exp Biol Med* 146(3):816-819, 1974.

Female Sprague-Dawley rats were injected i.v. with an emulsion containing 5 mg 7,12-dimethylbenzanthracene (DMBA). After most of the animals had developed mammary tumors, some were given 12 s.c. injections of 1 mg/day ovine prolactin (oPRL, 26 IU/mg). Six days later, the animals were killed and the specific binding of ^{125}I -oPRL in the excised tumors measured. The binding of prolactin to particulate membrane fragments in the total microsomal pellet was significantly correlated with the growth response of these tumors to prolactin administration. There was a negative correlation between the average growth response of all tumors in one rat and the amount of ^{125}I -oPRL specifically bound to the liver membranes of that animal. This or a similar method of determining prolactin dependence may be useful in assessing prolactin responsiveness in human breast cancer.

1255 MUTAGENICITY OF CHROMATES IN BACTERIA AND ITS RELEVANCE TO CHROMATE CARCINOGENESIS.

(E.) Venitt, S. (Inst. Cancer Res., Pollards Wood Res. Stat., Chalfont St Giles, England) and L. S. Levy. *Nature* 250(5466):493-495, 1974.

Escherichia coli B/r WP2 were incubated on agar plates with solutions of Na_2CrO_4 , K_2CrO_4 , and CaCrO_4 . All three chromates were equally effective in inducing statistically significant increases in the yield of prototrophic WP2 mutants. When bacteria in suspension were treated with Na_2CrO_4 , which was subsequently removed, the yield of induced revertants increased linearly with increasing chromate concentration; a similar degree of mutability was noted in *E. coli* WP2 and WP2uvrA strains, although the latter was slightly more sensitive to the cytotoxic effect of the chromate than was the former. Soluble salts of tungsten, molybdenum, zinc, cadmium, and mercury, and a soluble trivalent chromium compound, $\text{Cr}_2\text{SO}_4\text{K}_2\text{SO}_4\cdot 2\text{H}_2\text{O}$, gave negative results. The absence of the *exrA* repair pathway ('error-prone') and the *uvrA* repair pathway ('excision-repair') did not significantly modify the mutagenic response to hexavalent chromium. The reversion from tryptophan auxotrophy to prototrophy in this system involves mutation at an *ochre* triplet, UAA. It is likely that chromate does not modify AT base-pairs, but specifically attacks GC base-pairs, causing GC to AT transitions at a subsequent round of DNA replication.

1256 MOULDS, BACTERIA AND CANCER. (E.) Garner, C. (Dept. Exp. Pathol., U. Leeds, England).

New Sci 63(909):325-327, 1974.

A bacterial mutagenicity assay method for studying the activity of aflatoxins has been developed. When aflatoxin B₁, rat liver enzymes, and bacteria (strains of *Salmonella* species which required histidine for growth; mutated bacteria no longer need histidine)

were incubated together at 37 C, the bacteria were rapidly killed. Only organisms deficient in the DNA repair enzyme were sensitive. This indicated that killing was due to attack on the bacterial DNA by a metabolite of aflatoxin. Aflatoxin B₁ itself was not toxic to the bacteria, indicating that an aflatoxin B₁ metabolite was the toxic agent. Of the other naturally occurring aflatoxins, only those that are potent carcinogens were metabolized by the liver enzymes to toxic and mutagenic derivatives. When liver from several other species was tested for ability to convert aflatoxin B₁ to a toxic metabolite, it was found that all those tested, including human liver, could carry out this conversion. All aflatoxin-like molecules converted to toxic metabolites had a double bond at the 2,3-position. Such double bonds are converted to epoxides by liver enzymes. The epoxide formed during aflatoxin B₁ metabolism is postulated to react with bacterial DNA to induce mutations and with mammalian cell macromolecules to initiate the cancer process.

1257 HEPATOCARCINOGENIC MATERIAL IN URINE SPECIMENS FROM HUMANS CONSUMING AFLATOXIN.

(E.) Campbell, T. C. (Dept. Biochem. Nutrition, Virginia Polytech Inst. State U., Blacksburg), R. O. Sinnhuber, D. J. Lee, J. H. Wales and L. Salamat. *J Natl Cancer Inst* 52(5):1647-1649, 1974.

Urine extracts from children who had consumed peanut butter contaminated with aflatoxin B₁ (AFB₁, 21 µg/child/2 days) induced hepatomas in 22 of 78 rainbow trout when fed for a period of only 30 days. The amount of AFB₁ in the extracts was estimated to be equivalent to that contributed by the small quantity of AFB₁ excreted. The data suggest that the major fraction of aflatoxin ingested by humans is not excreted as aflatoxins B₁, M₁ or P₁ but as their relatively noncarcinogenic metabolites and conjugates.

1258 TRIAL OF A BACTERIAL SCREENING SYSTEM FOR RAPID DETECTION OF MUTAGENS AND CARCINOGENS.

(E.) Longnecker, D. S. (Dartmouth Med. Sch., N.H.), T. J. Curphey, S. T. James, D. S. Daniel and N. J. Jacobs. *Cancer Res* 3(7):1658-1663, 1974.

A bacterial test system which measures replication of a DNA polymerase-deficient strain of *E. coli* was used to study the mutagenic and carcinogenic potential of several newly synthesized nitrosamines, as well as several known carcinogens. The findings qualitatively agreed with those previously reported with this system, except that the zones inhibition in the present study were much smaller (not exceeding 2-4 mm). Azaserine, methanesulfonate, and methyl-nitrosourea inhibited growth without having to be metabolically activated (direct assay). In the presence of a crude rat and hamster liver microsomal-supernatant fraction, diethylnitrosamine, *O*-(*N*-nitroso-*N*-methyl-8-alanyl)-L serine, *O*-(*N*-nitrososarcosyl)-L-serine, acetylaminofluorine, melphalan, puromycin, and cycloheximide showed preferential inhibition of growth of the polymerase-deficient strain. None of

These substances showed activity in the direct assay system. Of several known carcinogens tested, only benzo(a)pyrene failed to inhibit growth of the polypyrase-deficient strain. The limitations encountered in this system suggest that it would not be very useful in screening chemicals for mutagenic and/or carcinogenic potential.

259 SARCOMA INDUCED IN RATS BY EXTRACTS OF PLANTS AND BY FRACTIONATED EXTRACTS OF *Krameria ixina*. (E.) O'Gara, R. W. (Nat'l. Cancer Inst., Bethesda, Md.), C. W. Lee, J. F. Morton, J. Kapadia and L. J. Dunham. *J Nat'l Cancer Inst* 2(2):445-448, 1974.

Extracts from the following plants, which are commonly taken internally by the natives of Curacao, are injected s.c. into the lower backs of female F1 black rats: *Acacia villosa*, *Annona glabra*, *Cajanus indicus*, *Capraria biflora*, *Heliotropium angiospermum*, *Mangifera indica*, *Melochia tomentosa*, *Mentelia aspera*, and three fractions of lyophilized *Krameria ixina*. Sarcomas developed after short latent periods in 100% of the rats which survived the toxic effects of treatment with *Acacia villosa* root. The root of *Melochia tomentosa* also produced sarcomas in 100% of the test animals, while *Heliotropium angiospermum* (without root) produced sarcomas in 75% of the rats. Sarcomas did not develop in animals treated with extracts from *Annona glabra*, *Cajanus indicus*, *Capraria biflora*, *Mangifera indica*, or *Mentelia aspera*. The aqueous extract of the whole *Krameria ixina* plant (without root) produced sarcomas in about 80% of the animals. No sarcomas were produced by the residue remaining after removal of the caffeine precipitates, sarcomas were produced in 67% of the rats treated with the alcohol extract; and sarcomas were produced in 23% of the rats treated with the residue from the aqueous extract after alcohol extraction. It is possible that the sarcomas produced by *Acacia villosa*, *Krameria ixina*, *Melochia tomentosa*, and perhaps some of the other plants, were attributable by tannin content of the plants.

260 3-METHYLCHOLANTHRENE-INDUCIBLE BINDING OF AROMATIC HYDROCARBONS TO DNA IN PURIFIED RAT LIVER NUCLEI. (E.) Rogan, E. G. (U. Nebraska Med. Ctr., Omaha) and E. Cavalieri. *Biochem Biophys Res Commun* 58(4):1119-1126, 1974.

Purified rat liver nuclei were incubated with (^{14}C) hydrocarbon, after which the nuclear DNA containing the bound hydrocarbon was isolated and purified. The purified liver nuclei were shown to contain enzymes which are capable of activating polycyclic aromatic hydrocarbons; the hydrocarbons can then bind to the nuclear DNA. When the rats were injected i.p. with 3-methylcholanthrene 24 hr prior to removal of their livers, the amount of hydrocarbon binding to the nuclear DNA was increased 4-fold. The omission of reduced nicotinamide adenine dinucleotide phosphate from the incubation mixtures resulted in a 4-fold decrease in the ability of the 3-methylcholanthrene induced nuclei to bind hydrocarbon to the

nuclear DNA. The most potent carcinogens in a series of seven hydrocarbons (in order of potency: 7,12-dimethylbenz(a)anthracene; benzo(a)pyrene; 3-methylcholanthrene; 7-methylbenz(a)anthracene; benz(a)anthracene; dibenz(a,h)anthracene; and anthracene) displayed a relatively greater extent of binding to the nuclear DNA. The data suggest that nuclear aryl hydroxylases affect the covalent binding of hydrocarbons to DNA and presumably initiate carcinogenesis.

1261 PRELIMINARY STUDY OF *IN VITRO* AFLATOXIN B_1 METABOLISM BY HUMAN LIVER. (E.) Merrill, A. H., Jr. (Dept. Biochem. Nutrition, Virginia Polytechnic Inst. State U., Blacksburg) and T. C. Campbell. *Toxicol Appl Pharmacol* 27(1):210-213, 1974.

(^{14}C)Aflatoxin B_1 (ring labeled) was incubated for 6.5 hr with 9000 g supernatant of human liver homogenate. The liver tissue was obtained at autopsy from a patient with a brain tumor and at biopsy from a patient with Hodgkin's disease. The chloroform extractable metabolites were quantitated by liquid scintillation counting following purification and identification by thin layer chromatography. The biopsy sample yielded, as percent of the initial concentration: aflatoxin B_1 , 15.4%; aflatoxin M_1 , 0.6%; and aflatoxin P_1 (free phenol), 1.3%. The autopsy sample yielded: aflatoxin B_1 , 11.9%; aflatoxin M_1 , 1.1%; aflatoxin P_1 (free phenol), undetected; and two aflatoxin metabolites less polar than aflatoxin B_1 , 0.9% and 1.7%. Thus, human liver appears to metabolize aflatoxin B_1 in a manner similar to that observed with experimental animals. However, in both animals and humans, a significant portion of aflatoxin B_1 metabolism remains unknown.

1262 MACROMOLECULAR SYNTHESIS FOLLOWING A SINGLE APPLICATION OF POLYCYCLIC HYDROCARBONS USED AS INITIATORS OF MOUSE SKIN TUMORIGENESIS. (E.) Slaga, T. J. (U. Wisconsin Sch. Med., Madison), G. T. Bowden, B. G. Shapas and R. K. Boutwell. *Cancer Res* 34(4):771-777, 1974.

After the application of initiating doses of polycyclic aromatic hydrocarbons, the incorporation of thymidine- ^3H , cytidine- ^3H , and leucine- ^3H into DNA, RNA, and protein, resp., in female Charles River CD-1 mouse skin epidermis was determined. Topical application of a single initiating dose (0.05 or 0.10 μM) of 7,12-dimethylbenz[a]anthracene depressed DNA synthesis for 24 hr, compared to controls, without a subsequent increase; there was no detectable epidermal hyperplasia, nor was RNA or protein synthesis altered. In contrast, 7,12-dimethylbenz[a]anthracene applied in sufficient quantity to result in tumor formation after a single dose (0.6 or 1.2 μM) caused a larger and more protracted inhibition of DNA synthesis, followed by a gradual increase above control level. Inflammation was evident at 6 days and, by 10 days after treatment, some visible wounding was observed and RNA and protein synthesis were stimulated. Initiating doses of 1,2,5,6-dibenz[a]anthracene gave results similar to initiating doses of DMBA; there was an early inhibition in DNA synthesis that was

not followed by a stimulation. 1,2,3,4-Dibenzanthracene, a weak or inactive initiating agent, produced a large peak of RNA synthesis at day 1, but DNA synthesis was close to control values at all times studied and, histologically, the skin sections appeared normal. 7,12-Dimethylbenz[a]anthracene, applied to skin in which DNA synthesis was stimulated 3-fold by acetic acid, blocked the increased incorporation of thymidine-³H into DNA.

1263 INHIBITION OF CARCINOGENIC AND TOXIC EFFECTS OF POLYCYCLIC HYDROCARBONS BY SEVERAL SULFUR-CONTAINING COMPOUNDS. (E.) Wattenberg, L. W. (U. Minnesota Med. Sch., Minneapolis). *J Natl Cancer Inst* 52(5):1583-1587, 1974.

Disulfiram, dimethyldithiocarbamate, and benzyl thiocyanate (0.03 mmole/g), when added to the diet, inhibited mammary tumor formation in Sprague-Dawley rats exposed to 7,12-dimethylbenz(a)anthracene (DMBA, 12 mg/ml by oral intubation). A single p.o. dose of disulfiram (100 mg) given 24 hr before the carcinogen similarly inhibited DMBA-induced mammary tumor formation. Adrenal necrosis from DMBA (30 mg/ml by oral intubation) was also inhibited by dietary disulfiram (0.03 mmole/g), dimethyldithiocarbamate (0.06 mmole/g), and benzyl thiocyanate (0.06 mmole/g). In A/HeJ mice, disulfiram (10 mg/g) prevented the occurrence of tumors of the forestomach that resulted from benzo(a)pyrene (0.3 mg/k) in diet but did not affect pulmonary adenoma formation in mice given the carcinogen (3 mg/ml) by oral intubation. The mechanism by which these sulfur-containing compounds inhibit carcinogenesis have not been determined.

1264 COMPARATIVE CHARACTERISTICS OF PENETRATION OF POLYCYCLIC HYDROCARBONS THROUGH THE PLACENTA INTO THE FETUS IN RATS. (Rus.) I. A. Shendrikova (N.N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR) and V. A. Aleksandrov. *Biull Eksp Biol Med* 77(2):77-79, 1974.

The following carcinogenic polycyclic hydrocarbons were administered p.o. through a stomach tube to non-inbred albino rats on the 21st day of pregnancy: 7,12-dimethylbenz(a)anthracene (DMBA), benz(a)pyrene (BP), and 3-methylcholanthrene (MC) in the form of a suspension in sunflower oil at a dose of 200 mg/kg. In experiments with DMBA, rats were sacrificed 5 and 30 min and 1-5 hr after administration. In experiments with MC and BP, rats were sacrificed after 3 hr. The content of polycyclic hydrocarbons was determined in washed fetuses and placentas and also in rat liver. Thin-layer chromatography was carried out and quasi-bright-line fluorescence spectra were recorded. A maximum accumulation of 1.53-1.6 µg of DMBA/g was observed in fetal tissues 2-3 hr after administration. By 5 hr after administration, only traces were observed. The ratio of DMBA concentration in liver, placenta, and foetus was 10:1.5:1 2 hr after administration. After 3 hr, significant quantities (2.77 µg/g) of BP had passed through the placenta into the foetus, whereas MC passed through only in trace quantities. The concentration of MC in rat liver (which has a rich blood

supply) was much lower and BP much higher than that of DMBA. It is concluded that absorption of MC from the gastrointestinal tract into the vascular system is much poorer than that of the other polycyclic hydrocarbons. A previous study showed that after i.v. injection of DMBA, the maximum accumulation in fetal tissues was observed after 1 hr and occurred between 45 and 60 min after administration. After p.o. administration the accumulation occurred for about 2 hr during the interval between 2 and 4 hr after administration. The total accumulation was approximately the same despite the fact that the i.v. dose was 24 mg/kg and the p.o. dose was 200 mg/kg.

1265 EFFECTS OF AN EPOXIDE HYDRASE INHIBITOR ON *IN VITRO* BINDING OF POLYCYCLIC HYDROCARBONS TO DNA AND ON SKIN CARCINOGENESIS. (E.) Burki, K. (Med. Coll. Georgia, Atlanta), T. A. Stoming and E. Bresnick. *J Natl Cancer Inst* 52(3):785-788, 1974.

1,1,1-Trichloro-2-propene oxide (TCPO) strongly inhibited the *in vitro* hydration of 3-methylcholanthrene (MCA)-11,12-oxide. It increased the nicotinamide-adenine-dinucleotide phosphate (NADPH)-dependent, microsome-catalyzed, *in vitro* binding of benzo[a]pyrene and MCA to DNA, presumably by increasing the effective concentration of metabolically formed active epoxide(s). Repeated topical administration of TCPO simultaneously with MCA (each 6 x 1.5 µM) to the skin of BALB/c mice markedly stimulated MCA-induced tumor formation. In view of the inhibitory effect of TCPO on the epoxide hydrase system *in vitro*, the higher carcinogenic potency of MCA in the presence of the hydrase inhibitor may be related to the inhibition of the MCA-oxide hydration reaction by TCPO and subsequent increase in the effective dose of the carcinogenic epoxide(s) *in situ*.

1266 CHROMOSOME STUDIES ON RAT LEUKEMIAS AND LYMPHOMAS, WITH SPECIAL ATTENTION TO FLUORESCENT KARYOTYPE ANALYSIS. (E.) Mori, M. (Fac. Sci. Hokkaido U., Sapporo, Japan) and M. Sasaki. *J Natl Cancer Inst* 52(1):153-160, 1974.

Chromosomes were studied in 9 primary and 14 transplanted Wistar-King A rat tumors, including 9 N-nitrosobutylurea (NBU)-induced leukemias, 6 Gross virus-induced lymphosarcomas, 3 Friend virus-induced lymphosarcomas, 4 Rauscher virus-induced lymphosarcomas, and 1 Dunning spontaneous leukemia. Among these, 8 primary and 6 transplanted tumors showed a diploid karyotype. One NBU-induced primary erythroblastic leukemia also had a diploid stemline and several hypotetraploid variants. The remaining 8 transplanted tumors were pseudodiploid, hyperdiploid, or hypodiploid, or a mixture of diploid and heteroploid; 1 exceptional case had a hypotetraploid stemline. The banding karyotype analysis revealed that the diploid tumors were indistinguishable from the normal rat somatic complex, except 1 case with minute structural changes. Other minor structural changes and markers were detected in some heteroploid tumors; the changes were not similar except for 2 transplanted Rauscher lymphomas that

(1267-1269)

showed either complete or partial trisomy for #1 chromosomes. Certain karyotypic transitions were observed in some tumors during prolonged *in vivo* or *in vitro* passages as well as in the metastatic process, but these changes were usually confined within the diploid range. By contrast, the Dunning leukemia, the oldest tumor in this series, exhibited drastic structural rearrangements with greater karyotypic variations. These observations indicate that the stemline cells of the rat leukemias and lymphomas are most stable at the diploid level.

1267 INFLUENCE OF NONSTEROID ANTI-INFLAMMATORY AGENTS ON PROTEIN SYNTHESIS AND HYPERPLASIA CAUSED BY A TUMOR PROMOTER. (E.) Scribner, J. D. (Fred Hutchinson Cancer Res. Ctr., Seattle, Wash.) and T. J. Slaga. *J Natl Cancer Inst* 52(6):1865-1868, 1974.

Promotion of tumors in skin of CD-1 mice by 12-*O*-tetradecanoylphorbol-13-acetate (TPA, 2 μ g) was reduced by treatment with either 1-phenyl-2-(*p*-hydroxyphenyl)-3,5-dioxo-4-*n*-butylpyrazolidine monohydrate (oxyphenbutazone, 1 mg) or 7-chloro-3,3a-dihydro-2H,9H-isoxazolo(3,2-*b*)(1,3)benzoxazin-9-one (W2354, 1 mg). Although oxyphenbutazone significantly reduced TPA-induced incorporation of tritiated precursors into cellular macromolecules, W2354 appeared to have a minimal effect on such incorporation. Similarly, oxyphenbutazone reduced TPA-induced enhancement of a specific protein in mouse epidermal cytosol to approximately control levels, but W2354 had no effect on this protein response. Neither compound affected gross inflammation produced by TPA, although oxyphenbutazone reduced histologically determined hyperplasia. The significance of selective protein induction in mouse epidermal cytosol as a marker for an effective promoter was further investigated by the determination of whether 15% acetic acid (inflammatory, hyperplasiogenic, but nonpromoting) or 50 μ g 3-methylcholanthrene (an efficient initiator) would produce the same protein induction found after TPA treatment. Neither produced a significant deviation from that found in untreated mice. It thus appears that a multitude of events contributes to effective tumor promotion, that inflammation and simple hyperplasia are inadequate for promotion, but that suppression of either inflammation or hyperplasia or TPA-induced alteration of genetic expression will result in some loss of promoting efficiency.

1268 EFFECTS OF THE IONIC ENVIRONMENT ON MODIFICATION OF YEAST TYROSINE TRANSFER RIBONUCLEIC ACID WITH N-ACETOXY-2-ACETYLAMINOFLUORENE. (E.) Pulkrabek, P. (Inst. Cancer Res., Coll. Phys. Surg., Columbia U., New York, N.Y.), D. Grunberger and I. B. Weinstein. *Biochemistry* 13(11):2414-2419, 1974.

The effects of Mg^{2+} and K^{+} ions on the modification of purified yeast tyrosine transfer RNA with N-acetoxy-2-acetylaminofluorene, a potent carcinogen which specifically binds to the 8 position of guanosine residues, were studied. In the presence of 3 mM Mg^{2+} and 0.1 M K^{+} , when the native form of tRNA is preserved, only 1.08 mol of the drug was bound per mol of tRNA.

After digestion of the modified tRNA with pancreatic ribonuclease, DEAE-cellulose chromatography of the resulting oligonucleotides, and Aminex A-6 separation of the component nucleosides, the major targets of the modification were two residues in the dihydro-uridine loop: 2'-*O*-methylguanosine at position 18 and guanosine at position 19. In addition, a minor target was found in a dinucleotide probably derived from the anticodon region. When the modification was performed in the absence of Mg^{2+} and K^{+} and in the presence of 3 mM EDTA, the binding of the drug increased to 1.6 mol/mol of tRNA. DEAE-cellulose chromatography of a pancreatic ribonuclease hydrolysate revealed, in addition to the previously described modifications, a modified tetranucleotide. The latter was presumably due to the modification of a guanosine at position 15, on the 5' side of the dihydrouridine loop. The amino acid acceptor activity of tyrosine tRNA modified in the presence of Mg^{2+} and K^{+} and in the presence of EDTA was decreased to 50% of that of the unmodified tRNA.

1269 INHIBITION BY DEXAMETHASONE OF INTRACELLULAR BINDING OF PHORBOL ESTERS TO MOUSE SKIN. (E.) Slaga, T. J. (Fred Hutchinson Cancer Res. Ctr., Seattle, Wash.), J. D. Scribner, J. M. Rice, S. B. Das and S. Thompson. *J Natl Cancer Inst* 52(5):1611-1618, 1974.

The binding of phorbol esters to Charles River mice epidermal subcellular fractions and the effect of tumor promoters on the protein complement of cytosol were investigated. When applied to mouse skin, ^{14}C -labeled 12-*O*-tetradecanoylphorbol-13 acetate (TPA, 17 nmoles; 2.6×10^5 cpm) and 3H -labeled 12-*O*-hexadecanoylphorbol-13 acetate (HPA, 16 nmoles; 2.3×10^6 cpm) remained associated, after extensive dialysis, with epidermal chromatin, cytosol, microsomes, and mitochondria. The specific activity of TPA and HPA binding to the subcellular fractions reached a peak by 1 hr after treatment. The powerful tumor promoter TPA had a greater affinity for the subcellular fractions than did the weaker promoter HPA. Simultaneous application of the antipromoting agent dexamethasone (225 nmoles) inhibited the binding to the cytosol and chromatin fractions from 1 to 24 hr after treatment but did not affect the other fractions. Label continued to be associated with cytosol protein after removal of unbound radioactivity by dialysis, gel filtration, and ultrafiltration. Polyacrylamide gel electrophoresis of the promoter-bound cytosol protein showed that most radioactivity was associated with the protein fraction previously reported to be a receptor for 3-methylcholanthrene. TPA and HPA binding to the cytosol receptor protein was inhibited between 3 and 12 hr after dexamethasone treatment. *In vitro* competition by a promoter or a nonpromoter for binding of radioactive TPA to the cytosol receptor protein correlated with promoting activity. However, dexamethasone did not compete *in vitro* for TPA binding to the cytosol receptor protein. When the protein complement of mouse epidermal cytosol was analyzed by electrophoresis on two different polyacrylamide gels, dexamethasone inhibited a slowly migrating fraction which was most enhanced between 12 and 24 hr

after treatment. The findings suggest that both the chromatin and cytosol fractions are involved in the early action of skin tumor promoters.

- 1270 HISTOGENESIS AND FINE STRUCTURE OF PERITONEAL TUMORS PRODUCED IN ANIMALS BY INJECTIONS OF ASBESTOS. (E.) Davis, J. M. G. (Inst. Occup. Hlth., Edinburgh, Scotland). *J Natl Cancer Inst* 52(6):1823-1837, 1974.

Primary tumors of the peritoneal cavity were produced in Wistar rats and mice BALB/c by the i.p. injection of crocidolite asbestos. Seventeen tumors were found in the 25 rats given 25 mg dust suspended in 1 ml distilled water and 20 tumors in the 60 mice given 10 mg suspended in 0.5 ml distilled water. The earliest discernible neoplastic stage consisted of many small, pedunculated nodules scattered over the surfaces of the viscera, diaphragm, and body wall. These nodules contained a central core of reticulin or collagen surrounded by layers of pleomorphic connective-tissue cells. The surfaces of the nodules were covered by a single layer of epithelial cells similar to normal mesothelium. In later stages some nodules remained distinct and became quite large, but often the tumor spread over the peritoneal surfaces as a uniform sheet. The cells found in sheets were mostly of the same type as those in large nodules: pleomorphic connective-tissue cells in the central regions and epithelial cells on the surface. In some advanced tumors, however, the cells had a spindle-cell pattern similar to a fibroma or fibrosarcoma. In this form the neoplasms were locally invasive; however, at earlier stages no signs of invasion could be detected. Electron microscope studies showed only a slight difference in ultrastructure between the different tumor cell types, and it is suggested that the growths arose from undifferentiated mesenchymal cells in the submesothelial tissues. These cells retained their normal pleomorphic pattern or gave rise to either epithelial (mesothelial) cells on free surfaces or spindle cells in deeper layers.

- 1271 PREVENTION OF BRONCHOPULMONARY CANCER. DETECTION OF HIGH-RISK SMOKERS BY COMPUTER AND STATISTICAL ANALYSIS. (Fr.) Zagury, D. (Fac. Med., Reims, France), A. Simatos and M. J. Faroux. *Bull Acad Natl Med* 157(7):588-594, 1974.

Preliminary results are presented for a bronchial cytological study made on 1146 smoking (83%) and non-smoking (17%) subjects, with the object of defining "high-risk" groups among apparently healthy asymptomatic subjects. Smears of phlegm were stained by the Papanicolaou method; alveolar and bronchial cells were observed. Bronchial lesions were classified as (1) typical simple metaplasia (normal cylindrical cells replaced by malpighian cells); (2) typical aggravated metaplasia (greater cell changes, especially in the nucleus and cytoplasm); (3) atypical metaplasia, considered a truly precancerous lesion (severe cell changes, without malignant characteristics). Variables studied included: daily and total consumption

of tobacco, age, age smoking began, other diseases, alcoholism, and exposure to occupational pollutants. Data were analyzed by statistical and computer methods. There was a significant difference between smokers and non-smokers in the frequency of typical simple metaplasia (57% and 39%, respectively), while the percentage of atypical metaplasia was not affected by usage vs non-usage. Total cigarette consumption per se had no major effect on simple metaplasia, although it is hypothesized that aggravated metaplasia may increase when consumption is about 4-5 cigarettes per day. Severe lesions appeared when total consumption was associated with other variables: early smokers had twice as many severe lesions; non-filter cigarettes contributed to the presence of severe lesions; and sex differences were not statistically significant. Chronic bronchial and lung diseases contribute to a "high-risk" diagnosis in subjects older than 55 yr, even if they did not smoke much; other "high-risk" categories were alcoholics and those exposed to occupational pollutants.

- 1272 EXPERIMENTAL PLASMACYTOMAS IN RELATION TO HUMAN MULTIPLE MYELOMA. (E.) Azar, H. A. (VA Hosp., Tampa, Fla.). *Ann Clin Lab Sci* 4(3):157-163, 1974.

Among animal models of plasma cell tumors, that induced in BALB/c mice by means of i.p. injections of oils remains the most reproducible and the most intensively studied. The BALB/c oil-induced and transplantable plasmacytomas resemble human myelomas in their ability to produce a monoclonal immunoglobulin or Bence Jones protein. Bence Jones type nephrosis in BALB/c mice closely mimics its human counterpart. There are also similarities in background of immunodeficiency and in antigen-binding affinity of monoclonal immunoglobulins, as well as in interesting interrelationships with malignant lymphomas. Unlike the BALB/c tumor model, human myeloma is principally a skeletal disease, not a gut-oriented or peritoneal plasmacytoma. The intriguing presence of intracisternal type A virus-like particles in BALB/c plasmacytoma cells and their absence in human myeloma is another major difference between the two forms of growth. The pathogenesis of human myeloma remains obscure, but the availability of experimental plasmacytoma models offers a means of systematically analyzing events leading to the neoplastic transformation of antibody-forming cells.

- 1273 AN AUTORADIOGRAPHIC STUDY OF NICKEL CARCINOGENESIS IN RATS FOLLOWING INJECTION OF $^{63}\text{Ni}_3\text{S}_2$ AND $\text{Ni}_3^{35}\text{S}_2$. (E.) Kasprzak, K. S. (Radiochem. Lab., Inst. Gen. Chem., Technical Inst. Poznan, Poland). *Res Commun Chem Pathol Pharmacol* 8(1):141-150, 1974.

Nickel subsulfide (Ni_3S_2) was synthesized from powdered nickel and sulfur and labeled with ^{63}Ni or ^{35}S by isotopic exchange. The $^{63}\text{Ni}_3\text{S}_2$ and $\text{Ni}_3^{35}\text{S}_2$ dusts (10 mg) were then administered to 37 Fischer rats by i.m. injection into both hind legs. The rats were

killed at intervals from 1 wk to 6 months after treatment and the organs and tissues were examined histologically and autoradiographically. Rhabdomyosarcomas were found in 50% or the rats killed during the fourth month postinjection and in 100% of the rats killed during the fifth and sixth months. Distant metastases were present in 25% of the tumor-bearing rats. Autoradiography indicated that extracellular Ni_3S_2 particles persisted at the site of injection without any apparent diffusion, dissolution, or translocation of ^{63}Ni or ^{35}S . Ni_3S_2 particles were observed infrequently within phagocytic cells at the site of injection. Intracellular localization of ^{63}Ni and ^{35}S was not detected within the muscle or tumor cells.

1274 PHYSICAL STUDIES OF N-ACETOXY-N-2-ACETYL-AMINOFLUORENE-MODIFIED DEOXYRIBONUCLEIC ACID. (E.) Chang, C. T. (Sch. Chem. Sci., U. Illinois, Urbana), S. J. Miller and J. G. Wetmur. *Biochemistry* 13(10):2142-2148, 1974.

Denatured T4 phage DNA was reacted with N-acetoxy-N-2-acetylaminofluorene. The rate of reaction was determined using the change in the melting temperature of the renatured DNA as an indicator of the percentage of modification. The renaturation rates of a series of modified DNAs were then investigated. This rate was reduced by a factor of two when the melting temperature was lowered by 15 C. The absorption at 305 nm, the negative circular dichroism band around 300 nm, the melting temperature change, and the buoyant density shift due to modification were also investigated. The data obtained indicated that the melting temperature change due to 1% modified base pairs was 0.9. Electric dichroism of the modified DNA was studied in an alternating field. From the dichroism, the angle between the aminoacetylfluorene residue 305-nm transition moment and the DNA helix was calculated as 60 ± 4 under conditions in which the 305-nm band was optically active. The aminoacetylfluorene residue must be located in an asymmetric potential field outside the DNA helix.

1275 ETHYLHYDRAZINE HYDROCHLORIDE AS A TUMOR INDUCER IN MICE. (E.) Shimizu, H. (Eppley Inst. Res. Cancer, Omaha, Nebraska), D. Nagel and B. Toth. *Int J Cancer* 13(4):500-505, 1974.

The lifetime administration of 0.0125% ethylhydrazine hydrochloride in drinking water to randomly bred Swiss mice, beginning at 7 wk of age, induced tumors of the lungs and blood vessels. Eighty-eight percent of the treated females and 62% of the treated males developed lung tumors, whereas among controls, the incidence was 21 and 23%, resp. In addition, the incidence of blood vessel tumors rose from 5 to 60% in females and from 6 to 16% in the males, compared to controls. The blood vessel tumors occurred most frequently in the liver, however, in a few cases, the spleen, ovary, lymph nodes and subcutis were also involved. The gross and light microscopic investigation of the tumors showed adenomas and adenocarcinomas of the lungs

and angiomas and angiosarcomas of the blood vessels of characteristic appearance. This investigation proves for the first time the tumorigenicity of this chemical. The hydrazine derivatives, as a class, are widespread in the environment, being used in industry, agriculture, and even medicine. Even though ethylhydrazine by itself is not known to have any specific purpose, it is part of β -phenylethylhydrazine, a well-known drug used to treat mentally depressed patients.

1276 TUMOR INDUCTION IN TRACHEAL GRAFTS: A NEW EXPERIMENTAL MODEL FOR RESPIRATORY CARCINOGENESIS STUDIES. (E.) Kendrick, J. (Carcinogenesis Program, Biol. Div., Oak Ridge Natl. Lab., Tenn.), P. Nettesheim and A. S. Hammons. *J Natl Cancer Inst* 52(4):1317-1325, 1974.

Tracheas from adult female Fischer 344 rats, male (C57BL/6 X C3H) F_1 mice, and male Syrian golden hamsters were grafted into the connective tissue of the backs of isogenic hosts. Most grafts were left on the hosts for 6-10 months, becoming vascularized within the first 2 wk. Four wk after implantation of the grafts, the following pellets were inserted into the grafted tissue: gelatin; 3 mg benzo(a)-pyrene (BP); 3 mg 3-methylcholanthrene (MCA); or 7, 25, or 50 mg crude cigarette smoke condensate (CSC). Instillation of the carcinogenic polycyclic hydrocarbons or CSC into the established grafts resulted in the development of hyperplasia, dysplasia, and squamous metaplasia within 4-7 days. In one study, invasive squamous cell carcinomas developed in 7 out of 13 grafts between 26 and 35 wk after the instillation of 5 mg of either MCA or BP. No tumors appeared in grafts into which 1 mg of N-nitrosomethylurea was inserted. Twenty-one days after pellet implantation, 1/3 of the initial BP dose remained in the graft. The tracheal transplant model appears to be a promising and versatile tool for studies of respiratory carcinogenesis.

1277 OXIDATIVE AND PHOTOCHEMICAL LINKAGE OF DIETHYLSTILBESTROL TO DNA *IN VITRO*. (E.) Blackburn, G. M. (Dept. Chem. Univ. Sheffield, England), A. J. Flavell and M. H. Thompson. *Cancer Res* 34(8):2015-2019, 1974.

The effect of long wavelength UV irradiation or of several oxidizing systems (iodine, hydrogen peroxide, or ascorbic acid) was studied on the degree of binding *in vitro* of ^{14}C -diethylstilbestrol (^{14}C -DES) to DNA. The degree of covalent binding of ^{14}C -DES to native and denatured DNA increased with increasing exposure to UV irradiation or to the oxidizing systems. Highest binding levels (≥ 1 molecule per 1000 bases) were achieved for UV irradiation and iodine-mediated binding. Covalently bound ^{14}C -DES could not be separated from DNA by organic solvent extraction, gel filtration chromatography or sucrose gradient ultracentrifugation. Gel filtration analysis of a depurinated ^{14}C -DES:DNA complex showed a 2:1 selectivity by DES for binding to purine rather than to pyrimidine bases.

1278 DYNAMICS OF THE CHANGE IN GLYCOLYSIS RATE AND THE CONTENT OF HEXOSOPHOSPHATES IN RAT LIVER HYALOPLASM DURING CARCINOGENESIS. (Rus.) Rubenchik, B. L. (Kiev Inst. Hyg. Nutrition, USSR). *Vopr Med Khim* 19(3):241-245, 1973.

Changes in the rate of glycolysis and hexosophosphate concentration in rat liver hyaloplasm were studied during p-dimethylaminoazobenzene (DAB)-induced carcinogenesis. Male albino rats of one group were fed a diet containing DAB, while group 2 (control) received a diet without the carcinogen. After 2 and 18 wk rats of both groups were sacrificed, the livers were removed and homogenized, and hyaloplasm was obtained after centrifugation of the homogenate. The increase in malonic acid concentration was determined spectrophotometrically in order to evaluate the rate of glycolysis. Glucose-6-phosphate (G-6-P), fructose-6-phosphate (F-6-P), fructose-1,6-diphosphate (F-1,6-DP) and 2-deoxyglucose-6-phosphate (DOGP) were determined. In the control, the rate of glycolysis was always higher when G-6-P rather than glucose was used as the substrate, which confirms earlier data on the limiting role of hexokinase in glycolysis. The high concentration of F-1,6-DP after addition of G-6-P is caused by glucose phosphate isomerase activity, which is essentially unchanged during carcinogenesis. The F-1,6-DP concentration in the system remained unchanged during carcinogenesis. Apparently an excess of hexose monophosphate facilitated an increase in phosphofructokinase activity which led to a gradual accumulation of F-1,6-DP. A gradual accumulation of DOGP was observed when 2-deoxy-D-glucose was added to the system. Addition of G-6-P to the system inhibited hexokinase, and synthesis of DOGP was reduced by almost two-thirds. A brief inhibition (5-10 min) of hexokinase by G-6-P was observed during carcinogenesis, but after 20 min the usual rate of glucose phosphorylation was restored. It is concluded that G-6-P does not control the rate of the hexokinase reaction in liver during carcinogenesis. After a 10-fold increase in the ATP concentration, the rate of glycolysis decreased by almost two-thirds when glucose was used and by more than 50% when G-6-P was added. Excess ATP in a control suppressed synthesis of F-1,6-DP as well as glycolysis. During carcinogenesis the rate of glycolysis and the increase in F-1,6-DP were almost identical at the usual concentration or with a 10-fold increase in ATP. Almost no changes in the rate of glycolysis and activity of glycolytic enzymes were noted in animals sacrificed after 2 wk.

1279 STRAIN-DEPENDENT TERATOGENIC EFFECTS OF 1-ETHYL-1-NITROSOUREA IN INBRED STRAINS OF MICE. (E.) Diwan, B. A. (Jackson Lab., Bar Harbor, Maine). *Cancer Res* 34(1):151-157, 1974.

Single i.p. injections of 1-ethyl-1-nitrosourea (0.5 mM/kg) were given to C57L/J, C57BL/6J, SWR/J, DBA/2J, and AKR/J mice on days 8 and 12 of gestation, and fetuses were examined on day 14, or after birth. High rates of fetal deaths were observed in C57L/J mice on day 14; observations on earlier days revealed an increase in the resorption rate and a concomitant decrease in the percentage of malformations from

days 10 to 14 of gestation, indicating that the early harmful effects of 1-ethyl-1-nitrosourea were incompatible with life. The 1-ethyl-1-nitrosourea induced a variety of fetal malformations at both day 8 and 12; the most common were of the brain and eyes, limbs, ribs, sternum, and vertebrae. The frequency and severity of these malformations varied with the stage of embryogenesis and the strain of mice. Strains C57L/J and C57BL/6J were most sensitive and strain AKR/J was most resistant; strains SWR/J and DBA/2J were intermediate.

1280 SELECTIVE ELIMINATION *IN VITRO* OF SENSITIVE CELL CLONES IN METHYLCHOLANTHRENE INDUCED SARCOMA BY VINBLASTINE SULPHATE. (E.) Trope, C. (Dept. Anat., U. Lund, Sweden). *Acta Pathol Microbiol Scand [A]* 82(3):419-426, 1974.

A short-term *in vitro* model was used to determine whether vinblastine sulfate could selectively eliminate cells sensitive to it. 3-Methylcholanthrene-induced murine sarcomas were incubated *in vitro* with vinblastine sulfate (100 µg/ml) and ³H-thymidine (2 µCi/ml); the effect of the drug was measured in terms of the incorporation of the tritiated thymidine into the drug-treated cells compared with nontreated control cells. In addition the transplantability of the cells into syngeneic female C57 black mice was determined after incubation with and without vinblastine sulfate. After inoculation of a fresh nontreated cell suspension, only a fraction of the injected cells grew and produced a tumor; after incubation for 4 hr without cytostatic drug, the number of cells producing tumor *in vivo* was reduced by about 90%. Incubation with vinblastine apparently resulted in a further loss of transplantability so that only approximately 4% of the cells remained transplantable after incubation. Incubation with vinblastine reduced the effect of vinblastine on cells obtained from tumors which had developed from incubated cell grafts. The data suggest that vinblastine sulfate treatment selectively eliminates "sensitive" cells and leaves "resistant" cells alive, resulting in a change in the composition of the tumor cell population.

1281 SUPPRESSION OF CHEMICALLY INDUCED PULMONARY TUMORS BY TREATMENT OF STRAIN A MICE WITH MURINE SARCOMA VIRUS. (E.) Stoner, G. D. (Sch. Med., U. California San Diego, La Jolla), A. J. Kniazeff, M. G. Shimkin and R. D. Hoppenstand. *J Natl Cancer Inst* 53(2):493-498, 1974.

Male and female A/He mice were given a single i.p. injection of 3-methylcholanthrene (MCA, 1 or 2 mg) or were treated with one or three i.p. inoculations of the Moloney strain of murine sarcoma virus (M-MSV, 10⁶ FFU) and MCA (1 or 2 mg). The percentage of mice with lung tumors (100%) was equivalent in the MCA and M-MSV + MCA groups. However, the average number of tumors/mouse was significantly lower in mice treated with M-MSV than in mice given only MCA. The percentage reduction in tumor incidence was 53% with 1 mg MCA and 28% with 2 mg. One dose of M-MSV

was as effective in inhibiting tumor induction as 3 doses. Treatment of mice with one i.p. injection of M-MSV (10^6 FFU) also significantly reduced the average number of lung tumors/mouse following i.p. administration of urethan (10 or 20 mg). The percentage reduction in tumor incidence was 55% with 10 mg urethan and 30% with 20 mg. All M-MSV-treated mice given 20 mg urethan had tumors compared with 83% of mice given 10 mg. M-MSV infection did not alter the incidence of spontaneous lung tumors, and the tumor response of males did not differ from that of females in treated or control groups. Histologically, all lung tumors were adenomas. Lesions (atypical granulomas) were present in the abdominal viscera, liver, and parietal pleural surfaces of 40% of M-MSV + MCA-treated mice and 5% of M-MSV + urethan-treated mice. No lesions were seen in mice treated with M-MSV only. Results show that the viral inhibition of M-MSV is independent of the virus dose but not of the dose of the chemical. The higher doses of MCA and urethan may have been immunosuppressive and thus reduced the immunostimulatory effect of the virus.

- 1282 ROUTE TO THE TRITIATION OF CARBON ATOM-9 OF CARCINOGENIC FLUORENYLHYDROXAMIC ACIDS. (E.) Gutman, H. R. (VA Hosp., Minneapolis, Minn.) and P. Bell. *J Labelled Compd* 10(2):255-270, 1974.

The selective tritiation of the methylene carbon atom of the carcinogens N-fluoren-3-yl- and N-fluoren-1-ylacetohydroxamic acid was investigated. The synthesis of N-[9- 3 H]fluoren-3ylacetohydroxamic acid involves hydrogenolysis of 3-aminofluoren-9-one to [9- 3 H]fluoren-3-amine with $\text{LiAl}^3\text{H}_4\text{-AlCl}_3$. The tritiated amine is oxidized to 3-nitro-[9- 3 H]fluorene with m-chloroperoxybenzoic acid and the labeled nitro compound is partially hydrogenated to the ^3H -hydroxamic acid with 10% Pd-C catalyst in the presence of acetic anhydride and triethylamine or dimethylaniline. N-[9- 3 H]fluoren-1-ylacetohydroxamic acid may be obtained from 1-aminofluoren-9-one by the same procedure. However, N-[9- 3 H]fluoren-2-ylacetohydroxamic acid cannot be prepared in this way because reduction of 2-aminofluoren-9-one with $\text{LiAlH}_4\text{-AlCl}_3$ does not proceed beyond the alcohol, 2-aminofluoren-9-ol.

- 1283 ACCUMULATION OF LABELLED AMINOTRIAZOLE IN SOME TRANSPLANTED TUMOURS IN MICE. (E.) Tjalve, H. (Dept. Toxicol. U. Uppsala, Sweden). *Br J Cancer* 30(2):136-141, 1974.

Autoradiography with ^{14}C -labelled aminotriazole (3-amino-1,2,4-triazole) was performed in mice with transplanted tumors. A high accumulation of radioactivity was demonstrated in the tumors at intervals from 1 hr to 5 days, the uptake being the highest in the actively growing parts. In relation to other tissues in the body, the uptake of radioactivity was higher in mammary carcinoma and fibrosarcoma than in lymphoma. There was also a general accumulation of radioactivity in the other tissues with rapid cell turnover, suggesting a possible participation in purine synthesis.

- 1284 TWO-STAGE TRANSFORMATION *IN VITRO*. (E.) Bateman, A. J. (Petersen Lab., Manchester, England) and C. Lasne. *Nature* 251(5472):257, 1974.

In a letter, Dr. Bateman questions the interpretation of results reported by Lasne *et al* (*Nature* 247:490, 1974) in which they showed an increased rate of transformation of rat fibroblast cultures following treatment by benzo(a)pyrene (BP) (initiator) and a phorbol ester (promoter). He states that since cultures were treated at the third passage but did not show a dramatic increase in the percentage of transformed colonies until the 34th passage, the "increased" transformation merely reflects selection of already transformed clones in a mixed population. The phorbol increased the selective advantage of transformed cells by 50%, and there was thus no sign of two-stage transformation. In his reply, Dr. Lasne states that the problem is not so simple, citing papers supporting the interpretation that the results confirm the beginning of an *in vitro* spontaneous transformation. Previous studies have failed to demonstrate selection of pre-existing transformed cells in such systems. The results with phorbol ester were interpreted in correlation with the established *in vivo* model in which promoter increases the tumor incidence and shortens the latent period in previously initiated animals.

- 1285 SEQUENTIAL CYTOLOGICAL CHANGES DURING DEVELOPMENT OF RESPIRATORY TRACT TUMORS INDUCED IN HAMSTERS BY BENZO(a)PYRENE-FERRIC OXIDE. (E.) Schreiber, H. (Oak Ridge Natl. Lab., Tenn.), G. Saccomanno, D. H. Martin and L. Brennan. *Cancer Res* 34(4):689-698, 1974.

The exfoliative cytology of the lung was studied during the induction and early development of respiratory tract tumors. Syrian golden hamsters received multiple intratracheal injections of benzo(a)pyrene- Fe_2O_3 for 14 wk at a cumulative dose of 45 mg benzo(a)pyrene. Shortly after start of the experiment a severe cytological response to the carcinogen application was observed. This response, characterized by large numbers of polymorphonuclear leukocytes and pulmonary macrophages containing Fe_2O_3 particles, rapidly diminished during further injections and disappeared after cessation of carcinogen administration. The average time interval from start of carcinogen application to death was 35.5 wk. During this time specimens revealed a progression from mild atypia of squamous metaplastic cells, to moderate atypia, to marked atypia, to changes indicative of cancer. These carcinogen-induced progressive cytological changes showed striking morphological similarities to cytological changes described in cigarette smokers prior to the development of lung cancer. By the 25th wk of the experiment, specimens of all carcinogen-treated animals had cells suggestive or conclusive of cancer. In animals that died after the 35th wk, the diagnosis of cancer had been made at an average time of 19 wk before death, while in animals that died between the 18th and 35th wk of the experiment the diagnosis had not been made earlier than 9 wk before death.

- 1286 THE MUTAGENICITY AND DNA-MODIFYING EFFECT OF HALOALKANES. (E.) Brem, H. (Coll. Phys. Surg., Columbia U., New York, N.Y.), A. B. Stein and H. S. Rosenkranz. *Cancer Res* 34:2576-2579, 1974.

A series of haloalkanes were tested for their ability to inhibit the growth of normal (pol A⁺) and DNA polymerase I-deficient (pol A₁⁻) *Escherichia coli*. These compounds were also tested for the mutagenic effects on *Salmonella typhimurium*. All of the haloalkanes examined preferentially inhibited the growth of the pol A₁⁻ strain of *E. coli*. The bromoalkanes appeared to be more active than their chloro analogs (e.g., 1,2-dibromoethane (1,2-DBE) was more active than 1,2-dichloroethane (1,2-DCE) and tetrabromoethane was more active than tetrachloroethane). The mixed haloethane 1-bromo-2-chloroethane had an activity intermediate to those of 1,2-DBE and 1,2-DCE. When the bromine was on the same carbon, the biological activity was enhanced (1,1-DBE was more active than 1,2-DBE), although when the halogens were on different carbon atoms, the distance between them had no effect on the activity. All of the haloalkanes tested, with the exception of 1,1,2,2-tetrabromoethane, were mutagenic for *S. typhimurium* TA 1530 and TA 1535. The number of mutations was related to the amount of reagent added, the rate of diffusion, and the size of the zone of growth inhibition. None of the substances tested induced mutations in *S. typhimurium* TA 1538. Since many of the compounds tested are widely used in industry and in the home, further determination of their potential hazard to health is indicated.

- 1287 DIFFERENTIAL SENSITIVITY OF THE DEVELOPING MOUSE EMBRYO TO MORTALITY, MALFORMATION AND NEOPLASMS INDUCED BY URETHANE (E.) Nomura T. (Osaka U. Med. Sch., Japan). *Biochim Soc Trans* 2(4):710-713, 1974.

The effect of urethane on embryonic death, malformation, and neoplasm formation was studied in pregnant ICR/JI mice at different times during gestation. The incidence of embryonic deaths and malformations showed a sharp threshold response, having maximal response (25-90%) at 1.5 mg/g maternal body wt and virtually no response at 1.0 mg/g. The incidence of preimplantation deaths and neoplasms, however, showed a definite dose response relationship. The sensitivity of embryonic lung to neoplasm formation by urethane varied inversely with the degree of differentiation of the lung tissue between days 13-19 of gestation. Tumors were also observed in offspring of mice exposed to urethane during fetal growth or in the neonatal period. Offspring of pregnant mice injected with urethane shortly before birth had a higher tumor incidence than those born of mice injected early in gestation. Studies with ¹⁴C-urethane showed that the compound was rapidly cleared (within 24 hr) in adults and fetal mice, but was slowly cleared (150 hr) in newborn mice. Assuming that shortly before birth fetuses cleared urethane slowly as did newborns, the increased time of effective exposure of tissues of perinatal mice to urethane would account for the above finding.

- 1288 CHANGES IN THE NUCLEAR STRUCTURE DURING THYROID CARCINOGENESIS IN RATS. AN IMAGE ANALYSIS STUDY. (E.) Christov, K. (Cancer Res. Inst., Sofia, Bulgaria), G. Kiefer, R. Kiefer and W. Sandritter. *Beitr Pathol* 152(1):19-36, 1974.

The nuclear and chromatin structure of normal, hyperplastic, and neoplastic thyroid epithelial cells was studied using new methods for preparing semithin sections and for image analysis. Data acquisition for computerized image processing was accomplished by means of a scanning universal micro spectrophotometer. Thyroid cell proliferation and tumor growth were induced in Wistar rats after treatment with methylthiouracil (MTU, 0.1 solution in drinking water) for 20, 270, or 450-650 days. During the stage of diffuse and nodular hyperplasia, an increase in nuclear surface area with a decrease in (apparent) nuclear DNA content and DNA concentration was observed. The surface area and circumference ratio of the nucleus in various thyroid tumors were similar to those observed in controls. However, the DNA content and concentration in follicular carcinomas were reduced compared with those of controls and papillary carcinomas. In the MTU-treated animals (during the stage of diffuse and nodular hyperplasia and during tumor growth), a tendency toward reduction in the number of centrally located chromocenters was noted. Their surface area increased significantly only during nodular hyperplasia. However, no difference was found in the number, surface area, and circumference ratio of the chromocenters of the follicular, papillary, and trabecular carcinomas of the thyroid gland. The DNA concentration in the chromocenters was lower during nodular hyperplasia and in the follicular carcinomas than in the controls or papillary carcinomas. The changes in the total condensed chromatin were generally similar to those of the centrally located chromocenters alone. During nodular hyperplasia and in the follicular carcinomas, the surface areas and circumferences of the chromocenters were greater than those of the controls. The DNA concentrations decreased during nodular hyperplasia and in the follicular carcinomas, and increased in the papillary carcinomas. The difference in (apparent) DNA content between the follicular and papillary carcinomas may be due to a higher proliferation capacity in the papillary carcinomas or a difference in staining reactivity.

- 1289 TOXICOLOGY OF FLAVOURS AND FOOD ADDITIVES. (E.) Anonymous. *Flavour Ind* 5(7/8):147, 1974.

The 1973 Annual Report issued by BIBRA is summarized. Research reports issued during the year covered the toxicity of food colors, methylphenylcarbonyl acetate, dimethyl sulfide, quillaia extract, cychohexylamine hydrochloride, and sorbic acid. Expected UK legislation on flavoring would probably consist of a long list of permitted flavorings with maximum permitted levels prescribed for synthetic flavors in food. Specific projects discussed include a comparative study of the gavage mode of administration, which is used as a means of mimicking the ingestion of food

additives by man. The experiments were designed to compare the effects accompanying administration of the same dose of allyl alcohol by gavage in oil or water with those resulting from consumption in drinking water. Hepatic nodules induced by Ponceau MX have been subjected to detailed study, which showed that because of the secondary nature of this change, and of a hepatocellular carcinoma observed, the coloring cannot be classified as a carcinogen in the strict meaning of the term.

- 1290 RAT LIVER HISTONE MODIFICATIONS AND THEIR RELATIONSHIP TO DNA-DEPENDENT RNA POLYMERASE ACTIVITIES DURING α -HEXACHLOROCYCLOHEXANE INDUCED LIVER PROLIFERATION. (E.) Sarkander, H.-I. (Pharmacol. Inst., Free U., Berlin, Germany), M. Kemmerle and W. Brade. *Naunyn Schmiedeberg Arch Pharmacol* 284(1):39-53, 1974.

The time course of histone acetylation, methylation and phosphorylation during α -hexachlorocyclohexane (α -HCH) induced liver cell proliferation was studied and correlated with other biochemical events in rat liver caused by α -HCH. Both *in vitro* acetylation and methylation showed an initial increase one and two hr after α -HCH which obvious precedes the beginning of increased nuclear *in vitro* RNA synthesis. Separation of *in vitro* acetylated liver histones isolated one and two hr after α -HCH application results in preferential accumulation of radioactive acetate in the range of F3, F2b, F2a2 histone fractions and in F2a1. A second peak of increased histone acetylation at 24 hr and methylation at 36 hr occurs during a period of increased nuclear RNA-polymerase activities and the beginning increase of DNA synthesis. An increased *in vitro* histone phosphorylation was measured 42 hr after α -HCH application. From the different time courses of these nuclear events it seems possible that the early histone acetylation and methylation might be involved in the beginning increase of transcriptional activity.

- 1291 INHIBITORY EFFECT OF *CAPSELLA BURSA-PASTORIS* ON HEPATOCARCINOGENESIS INDUCED BY 3'-METHYL-4-(DIMETHYLAMINO)AZOBENZENE IN RATS. (E.) Kuroda, K. (Res. Inst. Chemobiodynamics, Chiba U., Japan), M. Akao, M. Kanisawa and K. Miyaki. *Gann* 65(4):317-321, 1974.

The herb extract of *Capsella bursa-pastoris* (Cruciferae) was examined for its effect on hepatocarcinogenesis in rats fed 3'-methyl-4-(dimethylamino)azobenzene (3'-Me-DAB). Male Donryu rats were given 0.5 g 3'-Me-DAB by being fed a diet containing 0.06% 3'-Me-DAB for about 50 days, after which they were given drinking water containing the herb extract in 0.2% concentration with a basal diet for 258 days. Hepatocarcinomas developed in 10 of 12 control rats fed 3'-Me-DAB only. Administration of the herb extract to 10 animals brought a complete inhibition of hepatoma induction, accompanied by a markedly reduced development of cholangio-fibrosis, bile duct cell proliferation, and hepatic cell degeneration.

- 1292 MEMBRANE EFFECTS OF PHORBOL ESTERS. (E.) Wenner, C. E. (Roswell Park Mem. Inst., Buffalo, N.Y.), J. Hackney, H. K. Kimelberg and E. Mayhew. *Cancer Res* 34(7):1731-1737, 1974.

Tetradecanoyl-phorbol-acetate (TPA)-induced changes in membrane function and structure, reflected by changes in the activity of the ouabain-sensitive ($\text{Na}^+ + \text{K}^+$)-ATPase and in the electrophoretic mobility of hyperdiploid Ehrlich-Lettre ascites tumor cells (ELD), 3T3 fibroblasts, and beef brain microsomes, were studied. TPA (10^{-6} M) produced a 15% decrease in electrophoretic mobility of ELD cells. The decrease could be reversed by washing the cells in Ca^{++} free Krebs-Ringer phosphate. The mobility of ELD was unaffected by an inactive phorbol stereoisomer (4 α -phorbol-didecanoate). TPA failed to stimulate ($\text{Na}^+ + \text{K}^+$)-ATPase activity of ELD homogenates, rat glioma, or 3T3 cells, but did produce a 50% inhibition in beef brain microsome ATPase activity. TPA also failed to stimulate $^{86}\text{Rb}^+$ uptake by ELD or mouse skin sections. $^{86}\text{Rb}^+$ uptake in 3T3 cells was slightly stimulated by TPA.

- 1293 DIFFERENT BEHAVIOUR OF NORMAL AND CANCER CELL CULTURES CONCERNING THE BINDING OF 9,10-DIMETHYL-1,2-BENZANTHRACENE TO NUCLEAR ACIDS AND NUCLEAR PROTEINS. (E.) Amlacher, E. (Friedrich-Schiller-U., Inst. Pathol., Jena, East Germany). *Exp Pathol (Jena)* 9(1/2):79-87, 1974.

Embryonic murine fibroblasts, L-cells, and Ehrlich-ascites cells were incubated in culture with ^3H -9,10-dimethyl-1,2-benzanthracene (DMBA). Smear preparations of the isolated cell nuclei were subsequently subjected to lipid extraction and examined by autoradiography. The amount of DMBA and its metabolites in the normal fibroblasts was 11.4-fold higher than in the L-cells; the amount in the normal cells was also significantly higher than in the Ehrlich-ascites cells. The binding capacity of DMBA to the RNA, DNA and proteins of normal embryonic cells significantly surpasses that observed in transformed cells.

- 1294 A COMPARATIVE STUDY OF XENOBIOTIC-METABOLIZING ENZYMES IN LIVER AND INTESTINE OF VARIOUS ANIMAL SPECIES. (E.) Chhabra, R. S. (Nat'l. Inst. Environmental Hlth. Sci., Research Triangle Park, N.C.), R. J. Pohl and J. R. Fouts. *Drug Metab Disposition* 2(5):443-447, 1974.

Rats, mice, hamsters, guinea pigs, and rabbits were used in a preliminary study to select a model animal for more detailed study of xenobiotic-metabolizing enzymes in intestine. The xenobiotic oxidation reactions studied included hydroxylation of aniline, biphenyl, and benzpyrene and N-demethylation of ethylmorphine. NADPH-cytochrome c reductase activity and cytochrome P-450 were measured as parts of the microsomal electron transport system. The xenobiotic-metabolizing enzymes were present in livers of all the species and varied in activity

over a 2- to 6-fold range among species for any given enzyme. In intestines from mice, rats, guinea pigs, and hamsters, either some of the enzymes were absent or had very low activity which would require very sensitive methods for detection. The rabbit emerged as the best animal for studying intestinal microsomal xenobiotic metabolism since all xenobiotic-metabolizing enzymes studied were present in easily measurable quantities.

- 1295 STUDIES OF THE ACUTE AND LONG-TERM ORAL TOXICITY OF CHLORPYRIFOS (*O,O*-DIETHYL-*O*-(3,5,6-TRICHLORO-2-PYRIDYL) PHOSPHOROTHIOATE). (E.) McCollister, S. B. (Chem. Biol. Res., Dow Chem. USA, Midland, Mich.), R. J. Kociba, C. G. Humiston, D. D. McCollister and P. J. Gehring. *Food Cosmet Toxicol* 12(1):45-61, 1974.

The acute and chronic toxicity of p.o. chlorpyrifos (*O,O*-diethyl-*O*-(3,5,6-trichloro-2-pyridyl) phosphorothioate), a broad-spectrum insecticide, for a variety of laboratory animals was studied. The LD₅₀ values were 118-245 mg/kg in rats of both sexes, Dow-Wistar and Sherman, 2000 mg/kg in rabbits, 504 mg/kg in guinea-pigs, and 32 mg/kg in leghorn chicks. Rats and dogs were maintained on diets containing 0, 0.01, 0.03, 0.1, 1.0, or 3.0 mg/kg/day chlorpyrifos for 2 yrs (rats) or 12-15 months (dogs). In the dogs, plasma cholinesterase (ChE) activity was depressed by the three highest dosage levels, RBC activity was depressed by the two highest dose levels, and brain ChE activity was depressed slightly by the highest dose level. In the rats, brain ChE activity was depressed by the highest dose level. In neither species was there any evidence of an induction of cholinergic activity. Depression of the ChE activity was readily reversible by eliminating the insecticide from the diet. The chlorpyrifos treatment did not significantly affect the mortality, body weight, food intake, hematological or urinary parameters, organ weight, organ to body weight ratio, tumor incidence, or gross or histological appearance of the tissues in either rats or dogs. Thus, chlorpyrifos at dose levels of 0.1 and 0.03 mg/kg/day can be tolerated indefinitely by rats and dogs without any significant toxicological effects.

- 1296 HISTOCHEMICAL DEMONSTRATION OF THE BENZO-(*a*)PYRENE HYDROXYLASE ACTIVITY IN ANIMAL SKIN. (E.) Gati, E. (Intl. Agcy. Res. Cancer, Unit Environmental Carcinogens, Lyon, France), J. Y. Calop and F. Lafaverge. *Ann Histochim* 18(4):311-319, 1974.

The inducibility of the benzo(*a*)pyrene (BaP) metabolizing system in the skin was studied by applying benzo(*a*)anthracene to the shaved back skin of Sprague-Dawley rats and inbred Swiss mice. Mice were treated with 100 µg BaA in 0.2 ml acetone or 150 µg in 0.3 ml acetone, while rats received 1000 µg in 0.6 ml acetone. Alterations in skin, lungs, and liver brought about by the reduced pyridine nucleotide-dependent metabolic system were studied histochemically at intervals followed BaA treatment. Comparison

was made between the effects of BaA and those induced by i.p. methylcholanthrene (10 and 1 mg, resp. for rats and mice). The BaP metabolizing system in skin was shown to be localized in the epidermis and the lining epithelium of the hair follicles in both species. The enzyme-inducing effect of BaA was demonstrable 4 hr after topical application, the greatest reaction being seen at 48 hr. A positive histochemical reaction was also demonstrated in the livers of BaA treated animals. Quantitative measurements showed that BaP hydroxylase activity in rat skin was higher at 4 hr than at 48 hr. The specific activity of liver BaP hydroxylase activity was much higher, indicating the importance of this organ in the metabolism of topically applied BaA. BaP hydroxylase in skin and liver was also induced by methylcholanthrene.

- 1297 SCREENING OF COMPOUNDS STRUCTURALLY AND FUNCTIONALLY RELATED TO N-METHYL-N'-NITRO-N-NITROSOGUANIDINE, A GASTRIC CARCINOGEN. (E.) Endo, H. (Fac. Med., Kyushu U., Japan), K. Takahashi and H. Aoyagi. *Gann* 65(1):45-54, 1974.

A screening of compounds related to N-methyl-N'-nitro-N-nitrosoguanidine was attempted by examining the mutagenicity of various nitrosated guanidine derivatives for a strain of *Salmonella typhimurium* at neutral pH. Among the naturally occurring guanidines so far tested, nitrosated methylguanidine was the most mutagenic, nitrosated agmatine and γ-guanidinobutyric acid were moderately mutagenic, while nitrosated L-arginine and acetyl-L-arginine were weakly mutagenic. Regarding synthetic guanidines, nitrosated benzoyl-L-arginineamide, acetyl-L-arginineamide, and γ-guanidinobutyric acid amide showed a powerful mutagenic activity and were as active as or more so than nitrosated N-methyl-N'-nitrosoguanidine. Nitrosated L-arginineamide, β-guanidinopropionic acid, homoarginine, and benzoyl-L-arginine ethyl ester were weakly active. The mutagenic principle of nitrosated acetyl-L-arginine-amide was identified as N-nitroso-4-acetamido-4-carboxamidobutylcyanamide. The structural specificity involved in the mutagenicity of nitrosated guanidine derivatives is discussed in view of these findings.

- 1298 CELL PROLIFERATION AND PROMOTING ACTION IN SKIN CARCINOGENESIS. (E.) Raick, A. N. (U. Toronto Sch. Med., Ontario, Canada). *Cancer Res* 34(5):920-926, 1974.

Changes induced in the thickness, number of nucleated cell layers, and mitotic index of cells of female Swiss-Webster mouse interfollicular epidermis (IFE) by various doses (up to 0.06 mM) of ethylphenylpropionate (EPP) or turpentine were measured and their tumor promoting activity was tested. A maximal increase in the thickness and number of nucleated cell layers in the IFE was produced by 0.04 mM EPP and by 25-50% turpentine, doses which had minimal tumor promoting activity. Weekly application of EPP or turpentine to mouse skin following four weekly ap-

plications of a promoting dose of 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA, 0.0016 μ M), or 72 hr following treatment with a single dose, actually inhibited the tumor-promoting activity of TPA, even though maximal epidermal proliferation and hyperplasia were present. Skin treated with 50% turpentine, 25 μ g cantharidin, a nonpromoting dose of TPA, or 0.04 mM EPP showed an increased mitotic index in the IFE before the observed increase in the number of nucleated cell layers. Exactly the opposite sequence occurred following skin treatment with a promoting dose of TPA. These findings indicate a basic difference between the cellular reprogramming induced by promoting and nonpromoting agents.

1299 ARYL HYDROCARBON (BENZO(a)PYRENE) HYDROXYLASE IN HUMAN PERIPHERAL BLOOD MONOCYTES. (E.)

Bast, R. C. (Nat'l. Cancer Inst., Bethesda, Md.), J. P. Witlock, H. Miller, H. J. Rapp and H. V. Gelboin. *Nature* 250(5468):664-665, 1974.

Aryl hydrocarbon hydroxylase (AHH) is present in human peripheral blood monocytes and its activity is increased following treatment with benz(a)anthracene. In 12 different donors, AHH activity ranged from 0.3-1.4 U/10⁶ cells and increased 4- to 33-fold after incubation with benz(a)anthracene (1 μ g/ml). AHH from human peripheral blood monocytes has properties which are typical of the microsomal mixed-function oxygenases, i.e., a requirement for NADPH and inhibition by carbon monoxide. The presence of AHH in human peripheral blood monocytes implicates the reticuloendothelial system in the metabolism of polycyclic hydrocarbons, suggests one explanation for the immunogenicity of these compounds, and may provide a convenient assay for the study of AHH in human populations.

1300 HYDROXYMETHYLATION OF THE BENZENE RING. MICROSOMAL HYDROXYMETHYLATION OF BENZO(a)-PYRENE TO 6-HYDROXYMETHYLBENZO(a)PYRENE. (E.)

Sloane, N. H. (Dept. Biochem., U. Tennessee, Memphis) and T. K. Davis. *Arch Biochem Biophys* 163(1):46-52, 1974.

The formation of 6-hydroxymethylbenzo(a)pyrene from benzo(a)pyrene is shown to be catalyzed by sonicates of rat liver microsomes. The biosynthetic pathway for the formation of the aryl hydroxymethyl groups appears to be a direct hydroxymethylation of the benzene ring and does not involve 6-methylbenzo(a)-pyrene as an intermediate, because the formation of 6-hydroxymethylbenzo(a)pyrene is not a cytochrome P-450-mediated reaction, whereas a model aryl side chain methyl group hydroxylation is shown to be inhibited by cytochrome P-450 inhibitors. Hydroxymethylation of the benzene ring represents a new class of enzymatic reactions catalyzed by the liver. The full scope of this reaction and its metabolic significance as a possible metabolic route in the activation of carcinogenic polycyclic hydrocarbons is yet to be determined.

1301 PROBE ARSENIC LINK. (E.) Anonymous. *Chem Week* 115(11):20, 1974.

Stricter standards for worker exposure to arsenic-containing materials may be put into effect as a result of studies by Dow Chemical and Allied Chemical. The Dow study of 173 employees who had worked at an insecticide plant showed that 16.2% of the group exposed to arsenic compounds of lead, calcium, copper and magnesium died of cancer of the respiratory system, compared with 5.7% in a control group. Of 27 deaths from 1960 to 1972 of Allied employees or retirees who worked in a pesticide plant, 19 were caused by cancer: 10 lung cancer, three lymphatic and six of other types. In January, the National Institute for Occupational Safety and Health submitted criteria for a new exposure limit for inorganic arsenic: 0.05 mg/m³, compared with the current 0.5 mg. The AFL-CIO has not yet decided whether to request an emergency standard, as was done in the case of other suspected carcinogens. The Steelworkers Union believes that that standard for arsenic should be set at "no detectable level."

1302 FREQUENCY OF MAMMARY CELL DIVISION IN RELATION TO AGE: ITS SIGNIFICANCE IN THE INDUCTION OF MAMMARY TUMORS BY CARCINOGEN IN RATS. (E.) Nagasawa, H. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan) and R. Yanai. *J Nat'l Cancer Inst* 52(2):609-610, 1974.

³H-thymidine incorporation into the DNA of mammary glands in virgin Sprague-Dawley rats over a 2-hr period increased from 30 days to 50 days of age; it peaked at 50 days and declined abruptly after 70 days, in good correlation with well-known changes in the incidence of mammary tumors induced by polycyclic aromatic hydrocarbons. The degree of mammary development and the serum prolactin level (a potent stimulator of mammary tumor growth) were significantly lower at 30 days than after 50 days of age, but there were few differences in these measures between 50 and 110 days. Fifty-day-old rats given grafts of pituitaries at 30 days of age, in whom the incidence of carcinogen-induced mammary tumors was inhibited, showed significantly lower ³H-thymidine incorporation than did normal rats of the same age. These results suggest that mammary tumor induction by a carcinogen depends principally on the frequency of mammary cell division at the time a carcinogen acts on the gland.

1303 ENDOCERVICAL CHANGES WITH THE USE OF SYNTHETIC STEROIDS. (E.) Mingeot, R. (Clin. St. Michel, Brussels, Belgium) and C. Fievez. *Obstet Gynecol* 44(1):53-59, 1974.

Endocervical (106) biopsies taken from patients showing ectropion and colposcopic changes of vascular congestion and increased mucus secretion were studied histologically; the results were compared with those obtained from 73 cervical biopsies taken from patients with normal cycles. The endocervical samples were taken from patients being treated with ethinylestradiol combined with norethisterone or nor-

gestrel or mestranol combined with lynestrenol. The results indicated that the endocervical epithelium undergoes important changes under the influence of synthetic estroprogestatives. When at the maximum, these changes are unequaled in any other circumstance, even pregnancy. The frequency of metaplasia (21 of 106 cases) increases significantly under treatment. Adenomatoid hyperplasia was observed infrequently in the patients being treated with steroid hormones (2 of 106 cases). Cervical carcinoma *in situ* was diagnosed in two patients using estroprogestative contraceptives. Further observations must be made to determine the significance of the reported histologic changes.

1304 STRAIN DIFFERENCES IN THE INDUCTION OF SOLUBLE AND MICROSOMAL ENZYMES BY PHENOBARBITOL AND 3-METHYLCHOLANTHRENE. (E.) Jori, A. ('Mario Negri' Inst. Pharmacol. Res., Milan, Italy) and R. Pescador. *Chem Biol Interact* 8(5):297-302, 1974.

The ability of phenobarbital and 3-methylcholanthrene (3MC) to induce liver microsomal and soluble enzymes was studied in male and female Sprague-Dawley and Long-Evans rats. Phenobarbital strongly enhanced the V values for both aniline hydroxylase and aminopyrine N-demethylase in the Sprague-Dawley rats, but produced no modifications in the kinetics of the two reactions in the Long-Evans rats. 3MC increased the p-hydroxylation of aniline but did not affect the N-demethylation of aminopyrine; the effects were similar in both rat strains. 3MC increased the K_m for aminopyrine N-demethylation only in the Sprague-Dawley rats, however. The level of the liver microsomal enzyme cytochrome P-450 was similar for both strains under basal conditions and after 3MC treatment; however, phenobarbital induced a more marked increase in cytochrome P-450 in Sprague-Dawley than in Long-Evans rats. Phenobarbital considerably enhanced the activity of aldehyde dehydrogenase in the Sprague-Dawley animals but was completely inactive in Long-Evans rats. This difference was not related to a difference in the disposition of phenobarbital in the two strains.

1305 TRANSPLACENTAL EFFECTS OF 1-ETHYL-1-NITROSOUREA IN INBRED STRAINS OF MICE. IV. RAPID TUMOR INDUCTION IN STRAIN CROSSES. (E.) Diwan, B. A. (Jackson Lab., Bar Harbor, Me.), H. Meier and R. J. Heubner. *J Natl Cancer Inst* 52(3):893-895, 1974.

Reciprocal F_1 hybrids of AKR/J (resistant to 1-ethyl-1-nitrosourea (ENU) carcinogenicity) and SWR/J (susceptible to ENU carcinogenicity) mice were exposed to transplacental treatment with ENU on day 16 of gestation. The (SWR/J (female) X AKR/J (male)) F_1 offspring showed a high incidence of leukemia (79%) and pulmonary adenomas (93%) within 10 wk or less. The incidence of lung tumors was lower among the (AKR/J (female) X SWR/J (male)) F_1 offspring (50%) and the tumors occurred much later in life (16-30 wk). Thus, in the F_1 hybrids, susceptibility to tumorigenesis in the lung depends on the genotype of the mother. Although the incidence of leukemia was increased in the (AKR/J (female) X SWR/J (male)) F_1 mice (86%), its develop-

ment was delayed in comparison with the (SWR/J (female) X AKR/J (male)) F_1 offspring. No sex difference was observed in the incidence of lung tumors or leukemia in either group of F_1 hybrids. The spleens and lung tumors of both groups were positive for both type-C RNA tumor virus and its group-specific antigen. These findings are explained by the fact that AKR/J mice carry two dominant genes individually controlling group-specific antigen and virus expression.

1306 SEQUENTIAL EVENTS IN INDUCTION OF SARCOMAS BY 4-HYDROXYAMINOQUINOLINE 1-OXIDE: FIBROPLASIA, A PREMALIGNANT PHASE. (E.) Shurgin, A. (New York U. Sch. Med., New York City) and F. F. Becker. *J Natl Cancer Inst* 53(1):159-164, 1974.

Five mg of a DMSO solution containing 1 mg/ml of 4-hydroxyaminoquinoline 1-oxide (HAQO) was injected i.p. into 125 male Sprague-Dawley rats. In parallel experiments, rats were injected with either 7,12-dimethylbenz(α)anthracene (DMBA) or N-hydroxy-2-acetylaminofluorene (NOF). Thirty-four percent of the HAQO-injected rats died within 160 days, at which time the first mesodermal tumor was identified. Within the first 2 wk following HAQO administration, an intense inflammatory process was identified at the serosal and mesothelial surfaces of the liver, intestine, diaphragm, and other abdominal organs; this developed into a severe abdominal fibrogenesis. Within 14 months, 30% of the animals living longer than 160 days had developed sarcomas. In each case, the appearance of mesodermal tumors was preceded by moderate to severe abdominal fibrosis. Fifty percent of the tumors appeared to be fibrosarcomas, 11% were myosarcomas, 28% were mixed mesodermal sarcomas, and 11% presented a mixed mesodermal-epithelial appearance suggestive of a mesothelial origin. All of the tumors grew rapidly, with two fibrosarcomas metastasizing to the lung and five others spreading widely throughout the abdomen. Neither fibrosis nor sarcomas appeared in the NOF-treated rats; of the DMBA-treated animals, 5% showed rare, focal, fibrous adhesions and 1 of 90 developed an abdominal fibrosarcoma. The data suggest that an intense fibroplasia participated in the development of the malignant tumors in the HAQO-treated rats. HAQO may affect some multipotential mesenchymal cell which participates in the early reaction.

1307 INHIBITION BY CHLORAMPHENICOL OF AMINOAZO DYE CARCINOGENESIS IN RAT LIVER: RNA SYNTHESIS IN ISOLATED LIVER NUCLEI. (E.) Blunck, J. M. (Dept. Pathol., U. Melbourne, Australia), C. E. Crowther and N. P. Madsen. *Eur J Cancer* 10(1):1-11, 1974.

RNA synthesis was measured in isolated rat liver nuclei following pair-feeding of diets containing 0.06% 3'-methyl-4-dimethylaminoazobenzene (3'MeDAB), 2% chloramphenicol (CAP), or both 0.06% 3'MeDAB and 2% CAP for periods of 4 and 10 days to male Sprague-Dawley rats. At 4 days, there were significant increases in $Mn^{2+}/(NH_4)_2SO_4$ -stimulated activity in rats fed CAP or both 3'MeDAB and CAP and a significant increase in the Mg^{2+} -stimulated activity in rats fed 3'MeDAB and CAP relative to control rats. After 10 days of pair-

feeding, Mg^{2+} -stimulated RNA synthesis was increased in all the treated groups, being significantly greater in the group receiving both 3'MeDAB and CAP than in the group receiving 3'MeDAB alone. $Mn^{2+}/(NH_4)_2SO_4$ -stimulated RNA synthesis was significantly increased in the group receiving CAP. The RNA/DNA ratio of the isolated nuclei was increased in rats fed CAP and was greater in rats fed both 3'MeDAB and CAP than in rats fed 3'MeDAB alone. The increase in nuclear RNA synthesis in rats protected by concurrent administration of CAP as compared with rats fed the carcinogen is considered noteworthy and may be implicated in the protective effect.

- 1308 BINDING OF METABOLITES OF DIETARY 4-DIMETHYLAMINOAZOBENZENE AND 2-METHYL-4-DIMETHYLAMINOAZOBENZENE TO RAT LIVER DNA AND PROTEIN OF SUBCELLULAR FRACTIONS. (E.) Chauveau, J. (Inst. Sci. Res. Cancer, Villejuif, France), M. Meunier and A. Benoit. *Int J Cancer* 13(1):1-8, 1974.

The binding of metabolites of two related azo dyes of different carcinogenic potency, the carcinogenic 4-dimethylaminoazobenzene (DAB) and the weakly carcinogenic 2-methyl-4-dimethylaminoazobenzene (2-Me-DAB), to Sprague-Dawley rat liver DNA and to subcellular fraction protein was studied following chronic p.o. administration for 1-3 wk. DAB metabolites were bound to liver DNA to a higher extent than those of 2-Me-DAB. In contrast, the binding of 2-Me-DAB metabolites was equal to or higher than that of DAB metabolites to protein. The amount of protein-bound metabolites was studied on the nucleo-mitochondrial fraction, microsomes, supernatant, nuclei, chromatin, nucleoplasm, nucleolar fraction, and nuclear membrane. The supernatant bound the highest levels of DAB and 2-Me-DAB metabolites. The time course of binding of DAB metabolites to DNA and protein was different from that of 2-Me-DAB metabolites. These results show the possible involvement of carcinogen-DNA binding in the mechanism of carcinogenesis.

- 1309 EFFECT OF LONG-TERM EXPOSURE TO 1,1-DICHLORO-2,2-BIS(P-CHLOROPHENYL)ETHYLENE, TO 1,1-DICHLORO-2,2-BIS(P-CHLOROPHENYL)ETHANE, AND TO THE TWO CHEMICALS COMBINED ON CF-1 MICE. (E.) Tomatis, L. (Int. Agency Res. Cancer, Lyon, France), V. Turusov, R. T. Charles and M. Boicchi. *J Natl Cancer Inst* 52(3):883-891, 1974.

For their lifespan, 240 CF-1 mice were given 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) or 1,1-dichloro-2,2-bis(p-chlorophenyl)ethane (p,p'-DDD) or DDD at a dose level of 250 ppm or the two chemicals combined at a dose level of 125 ppm in the diet. The animals were observed until 130 wk of age, at which time the survivors in each group were killed. Exposure to p,p'-DDE resulted in a high incidence and early appearance of liver tumors, particularly in female mice. Exposure to p,p'-DDD moderately increased the incidence of liver tumors in males only and markedly increased the incidence of lung tumors in both sexes, whereas exposure to p,p'-DDE plus p,p'-DDD resulted in a marked increase in incidence and

early appearance of liver tumors in both sexes. The storage levels of these metabolites were higher in fat tissue than in the liver or kidneys, and the storage concentration of p,p'-DDE was higher than that of p,p'-DDD following the same exposure levels.

- 1310 IDENTIFICATION OF NEW WATER-SOLUBLE METABOLITES OF ACETANILIDE. (E.) Grantham, P. H. (Natl. Cancer Inst., Bethesda, Md.), L. C. Mohan, E. K. Weisberger, H. M. Fales, E. A. Sokoloski and J. H. Weisburger. *Xenobiotica* 4(2):69-76, 1974.

Seven-week-old male Fischer rats were maintained for four wk on a diet containing 0.8% 3H -acetanilide (0.129 mC/mM). Metabolites in urinary extracts were analyzed by paper, thin-layer, and DEAE-cellulose column chromatography, scintillation spectrometry, Raney nickel reactions, mass spectroscopy, and nuclear magnetic resonance. Two new urinary metabolites of acetanilide were identified as the mercapturic acid derivatives 3-[(5-acetamido-2-hydroxyphenyl)thio]-N-acetylalanine and 3-[5-acetamidophenylthio]-N-acetylalanine. They accounted for 7-10% and 1-3%, resp., of the urinary radioactivity. The data are consistent with a mode of formation involving an intermediate epoxide.

- 1311 BATTLE LINES DRAWN ON VINYL CHLORIDE ISSUE. (E.) Anonymous. *Chem Eng News* 52(8):16, 1974.

Controls on the occupational exposure to vinyl chloride or other chemicals used in making the monomer or in polymerizing it to polyvinyl chloride have been requested by the labor unions. These controls include no measureable exposure to the carcinogen, safer work practices, closed systems, use permits, periodic medical and lab tests, plus a cut of residual vinyl chloride in PVC resins to less than 0.01% (100 ppm). The deaths of four polymerization section workers at the Louisville, Ky. plant of B. F. Goodrich have been attributed to angiosarcoma of the liver. These workers had average exposures of some 19 yr to vinyl chloride and 10 yr to vinylidene chloride with variable exposure to vinyl acetate, methyl acrylate, ethyl acrylate, methanol and chlorinated solvents. Angiosarcoma of the liver is a rare occurrence, accounting for only 20 to 30 deaths/yr in the entire U.S., and can be misdiagnosed as cirrhosis of the liver. Liver angiosarcomas have been experimentally created in rats inhaling vinyl chloride down in the 250 ppm level. The rats also developed zymbal glands carcinomas and kidney nephroblastomas.

- 1312 CHANGES IN THE CONTENT OF FIBRINOGEN AND CORTICOSTEROIDS IN RAT BLOOD IN DEVELOPMENT OF EXPERIMENTAL CANCER IN THE LUNGS. (Rus.) Negrei, L. N. (Inst. Problems Oncol., Acad. Sci., Ukrainian SSR, Kiev), E. B. Sopotsinskaya, N. V. Balenko and M. I. Smelkova. *Fiziol Zh* 19(4):530-534, 1973.

- 1313 EXPERIMENTALLY INDUCED CANCER OF THE COLON IN RATS AND MICE. (E.) Ward, J. M. (Nat'l. Cancer Inst., NIH, Bethesda, Md.), R. S. Yamamoto, T. Benjamin, C. A. Brown and J. H. Weisburger. *J Am Vet Med Assoc* 164(7):729-732, 1974.
- 1314 EFFECTS OF LYOPHILIZATION AND STORAGE OF RAT LIVER MICROSOMES ON ACTIVITY OF ANILINE HYDROXYLASE, CONTENTS OF CYTOCHROME b_5 AND CYTOCHROME P-450 AND ANILINE-INDUCED P-450 DIFFERENCE SPECTRUM. (E.) Kamataki, T. (Fac. Pharm. Sci., U. Chiba, Japan) and H. Kitagawa. *Jap J Pharmacol* 24(2):195-203, 1974.
- 1315 FORMATION OF NITROSAMINES IN FOOD. (E.) Schoental, R. (Roy. Vet. Coll., U. London, England). *Food Cosmet Toxicol* 12(1):167-169, 1974.
- 1316 A METHOD FOR THE DESTRUCTION OF NITROSAMINES IN SOLUTION. (E.) Gangolli, S. D. (Br. Ind. Biol. Res. Assoc., Surrey, England), W. H. Shilling and A. G. Lloyd. *Food Cosmet Toxicol* 12(1):168, 1974.
- 1317 STEROID METABOLISM BY HUMAN BREAST AND RAT MAMMARY CARCINOMATA. (E.) Miller, W. R. (U. Edinburgh Med. Sch., Scotland), A. P. M. Forrest and T. Hamilton. *Steroids* 23(3):379-395, 1974.
- 1318 EARLY HYPERPLASTIC LESION OF BLADDER OBSERVED IN MAN EXPOSED TO 1-NAPHTHYLAMINE. (Jap.) Ishizu, S. (Tokyo Women's Med. Coll., Japan), M. Minami, K. Yamamura, T. Umezu and M. Yoshida. *Jap J Cancer Clin* 19(12):1199-1201, 1973.
- 1319 ANALYSES OF DIFFERENTIAL SENSITIVITIES OF SYNCHRONIZED HELA S3 CELLS TO RADIATIONS AND CHEMICAL CARCINOGEN DURING THE CELL CYCLE: (II) ULTRAVIOLET LIGHT. (E.) Watanabe, M. (Fac. Pharm. Sci., Kanazawa U., Japan) and M. Horikawa. *Biochem Biophys Res Commun* 58(1):185-191, 1974.
- 1320 AFLATOXIN B_1 METABOLISM BY RAINBOW TROUT (*SALMO GAIARDNERI*). (E.) Schoenhard, G. L. (Oregon State U., Corvallis). *Diss Abs Int B* 35(2):706-B, 1974.
- 1321 BENZO(a)PYRENE-STIMULATED DNA SYNTHESIS IN HAMSTER EMBRYO CELLS. (E.) Mironescu, S. (Thomas Jefferson U., Philadelphia, Pa.) and R. Love. *Proc Am Assoc Cancer Res* 15(March):1, 1974.
- 1322 EFFECTS OF BLEOMYCIN OR ENDOXAN ON UTERINE CERVICAL CARCINOMA OF MICE INDUCED BY 20-METHYLCHOLANTHRENE, AND *IN VITRO* STUDIES ON UTERINE BODY ADENOCARCINOMA OF RATS INDUCED BY 7,12-DIMETHYLBENZ(a)ANTHRACENE. (E.) Wang, F.-C. (Fac. Med. Chiba U., Japan). *Acta Obstet Gynaecol Jap* 19(3):212, 1972.
- 1323 VALUE OF FREE METAPHASE CELL PREPARATIONS IN CYTOPHOTOMETRIC STUDY OF EXPERIMENTAL SKIN CARCINOGENESIS. (E.) Alavaikko, M. (Dept. Pathol., U. Oulu, Finland). *Acta Pathol Microbiol Scand(A)* 82(1):145-152, 1974.
- 1324 EXPERIMENTALLY INDUCED MALIGNANT NEURINOMAS AS TRANSPLANTABLE TUMORS. MORPHOLOGY AND *IN VITRO* BEHAVIOUR. (E.) Mennel, H. D. (Max Plank Inst. Brain Res., Ostermerheimer, Germany) and J. Bucheler. *Acta Neuropathol* 27(2):153-161, 1974.
- 1325 EMBRYONIC EFFECTS OF FEEDING BRACKEN FERN (*PTERIDIUM AQUILINUM*) TO PREGNANT MICE. (E.) Yasuda, Y. (Fac. Med., Kyoto U., Japan), T. Kihara and H. Nishimura. *Toxicol Appl Pharmacol* 28(2):264-268, 1974.
- 1326 CHEMICALLY INDUCED DIFFERENTIATION IN A METHYLCHOLANTHRENE RHABDOMYOSARCOMA. (It.) D'Ancona, S. (Dept. Chem., Clin. Microscopy, U. Padova, Italy). *Acta Chir Ital* 29(1):105-119, 1974.
- 1327 EFFECT OF THE CARCINOGEN DIMETHYLNITROSAMINE ON HETEROLYSOSOME FUNCTION IN ADULT MICE. (E.) Farb, R. M. (Dept. Biol., U. Alabama, University) and J. L. Mego. *J Reticuloendothel Soc* 15(6):6a, 1974.
- 1328 INTERACTIONS OF CARCINOGENS ON LIVER ENZYMES. (E.) Lotlikar, P. D. (No affiliation) and M. B. Wasserman. *Food Cosmet Toxicol* 12(1):155-156, 1974.
- 1329 LOCALIZATION OF 3H -BENZPYRENE IN THE CELLS OF *XENOPUS LAEVIS* EMBRYOS. (E.) Csaba, G. (Semmelweis U. Med., Budapest, Hungary), N. K. Do and S. U. Nagy. *Z Mikrosk Anat Forsch* 88(1):80-84, 1974.
- 1330 CHANGES IN RAT LIVER NUCLEAR PROTEIN METABOLISM FOLLOWING A SINGLE CARCINOGENIC DOSE OF DIETHYLNITROSAMINE. (E.) Gronow, M. (U. Leeds, Sch. Med., England) and G. Griffiths. *Exp Pathol* 9(1/2):73-78, 1974.
- 1331 THE INFLUENCE OF THE RHYTHM OF CYCLOPHOSPHAMIDE ADMINISTRATION ON THE ANTITUMOUR EFFECT AND IMMUNE RESPONSE OF MICE WITH SARCOMA INDUCED BY METHYLCHOLANTHRENE. (Rus.) Gordienko, S. P. (P. A. Guertsen Res. Inst., Moscow, USSR), V. M. Bergoltz and K. V. Botsmanov. *Biull Eksp Biol Med* 78(7):87-90, 1974.
- 1332 EFFECTS OF STRESS ON GROWTH OF TRANSPLANTED AND 7,12-DIMETHYLBENZ(a)ANTHRACENE-INDUCED TUMORS AND THEIR MODIFICATION BY PSYCHOTROPIC DRUGS. (E.) Pradhan, S. N. (Howard Univ. Coll. Med., Washington, D.C.) and P. Ray. *J Natl Cancer Inst* 53(5):1241-1245, 1974.

1333 A DETERMINATION OF 3-OXYANTHRANILIC ACID AS A HAPTEN IN BLOOD OF PERSONS WORKING IN CONTACT WITH ANILINE DYES. (Rus.) Skachkov, A. P. (USSR Min. Publ. Hlth., Leningrad). *Vopr Onkol* 20(5):50-53, 1974.

1334 ELEVATION OF THE THRESHOLD OF SENSITIVITY OF THE HYPOTHALAMO-PITUITARY SYSTEM TO HOMEOSTATIC EFFECT OF ESTROGENS BY CARCINOGENS. (Rus.) Anisimov, V. N. (USSR Acad. Med. Sci., Leningrad) and V. M. Diljman. *Vopr Onkol* 20(5):61-66, 1974.

1335 PROLIFERATIVE LESIONS IN CHEEK POUCH AND ESOPHAGUS OF HAMSTERS TREATED WITH PLANTS FROM CURACAO, NETHERLAND ANTILLES. (E.) Dunham, L. J. (Natl. Cancer Inst., Bethesda, Md.), R. H. Sheets and J. F. Morton. *J Natl Cancer Inst* 53(5):1259-1269, 1974.

1336 INHIBITORY EFFECT OF POLYCHLORINATED BIPHENYLS ON LIVER TUMORIGENESIS IN RATS TREATED WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE, N-2-FLUORENYLACETAMIDE, AND DIETHYLNITROSAMINE. (E.) Makiura, S. (Nara Med. Univ., Kashihara, Japan), H. Aoe, S. Sugihara, K. Hirao, M. Arai and N. Ito. *J Natl Cancer Inst* 53(5):1253-1257, 1974.

1337 HEPATIC CARCINOGENESIS OF AFLATOXIN M₁ IN RAINBOW TROUT (*SALMO GAIRDNERI*) AND ITS ENHANCEMENT BY CYCLOPROPENE FATTY ACIDS. (E.) Sinnhuber, R. O. (Dep. Food Sci. Tech., Oregon State Univ., Corvallis), D. J. Lee, J. H. Wales, M. K. Landers and A. C. Keyl. *J Natl Cancer Inst* 53(5):1285-1288, 1974.

1338 INHIBITION OF MAMMARY DYSPLASIA IN ESTROGEN-TREATED C3H/HEJ FEMALE MICE BY SUPPRESSION OF PROLACTIN SECRETION. (E.) Brooks, C. L. (Dept. Anat., Michigan State U., East Lansing) and C. W. Welsh. *Proc Am Assoc Cancer Res* 15(March):1, 1974.

1339 MEASUREMENT OF EPIDERMOID CARCINOMA DEVELOPMENT INDUCED IN THE LUNGS OF RATS BY 3-METHYLCHOLANTHRENE-CONTAINING BEESWAX PELLETS. (E.) Hirano, T. (Natl. Cancer Inst., Bethesda, Md.), M. Stanton and M. Layard. *J Natl Cancer Inst* 53(5):1209-1219, 1974.

See also:

* (Rev): 1201, 1202, 1203, 1204, 1205, 1206, 1219, 1226
* (Immun): 1461, 1464, 1466, 1467, 1479, 1488, 1505
* (Epid-Biom): 1573, 1579, 1580, 1587, 1596, 1616

- 1340 RADIATION-INDUCED HEAD AND NECK TUMOURS. (E.) Modan, G. (Chaim Sheba Med. Ctr., Tel Hashomer, Israel), H. Mart, D. Baidatz, R. Stein-itz and S. G. Levin. *Lancet* (7852):277-279, 1974.

Delayed radiation effects were studied in a retrospective follow-up of 10,902 Israeli children which had been irradiated (75-100 kV) for *tinea capitis*, a fungal scalp infection, between 1949 and 1960. For each case, one or two controls were also studied. There was a significant increase of both malignant and benign neoplasms in the irradiated group, as compared to the controls. This increased risk was limited to head and neck neoplasms, the most striking increase being seen in brain, parotid, and thyroid tumors. There was also a slight, but statistically nonsignificant, increase in leukemia among the irradiated group. The interval between first scalp irradiation and tumor diagnosis indicated a fairly long incubation period. This is believed to be the first definite demonstration of the role of ionizing radiation in the etiology of brain tumors in man.

- 1341 RADIATION CANCER IN JAPANESE RADIOLOGICAL WORKERS. (E.) Kitabatake, T. (Niigata U., Sch. Med., Japan), T. Watanabe and S. Koga. *Strahlentherapie* 146(5):599-606, 1973.

There were 83 deaths caused by professional exposure to radiation in Japan, the data of which are complete and available in 30 cases of skin cancer, 28 leukemias, 7 aplastic anemias, and 9 other diseases. In skin cancer the age of death was widely distributed and not much different from that of skin cancer occurring in the general male Japanese in 1970. The latent period ranged from 3 to 44 yr, the average being 22.2 yr, which is nearly the same as seen in skin cancer in radiotherapeutic patients. Data indicated that the larger the initial three yr dose level, the shorter the latent period and the younger the age of onset of cancer. For leukemia the average latent period was 17.67 yr. No correlation between the total dose and the length of the latent period could be observed. When classed into three dose levels, cases of acute type more frequently occurred in low dose classes (under 100R). The average latent period for onset of aplastic anemia was 19.1 yr. No definite correlation was seen between latent period and total dose, although the group examined was relatively small in number.

- 1342 AUTOPSY STUDY OF BLAST CRISIS IN PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA, HIROSHIMA AND NAGASAKI, 1949-1969. (E.) Liu, P. I. (Dept. Path., Kansas U. Med. Ctr., Kansas City), T. Ishimaru and D. H. McGregor. *Cancer* 33(4):1062-1067, 1974.

Twenty-three cases of chronic granulocytic leukemia (CGL) with terminal blast crisis were found among 101 cases of CGL autopsied in Hiroshima and Nagasaki between 1949 and 1969. There was no significant evidence of a relationship between whole body radiation at the time of the atom bomb explosion (ATB) and the

development of blast crisis. Although blast crisis occurred more frequently during the later years of the study, this tendency was not significant. The incidence of blast crisis did not vary significantly with age or sex (it correlated with the 2:1 male:female ratio for CGL). Gross hemorrhage was more frequent in the brain, skin, kidneys, lungs, and gastrointestinal tract in patients with blast crisis, the increase being significant in the case of the lungs and gastrointestinal tract. Leukemic cell infiltration in histologic sections of various tissues was more frequent in patients with blast crisis, this being statistically significant from the kidneys, gastrointestinal tract, and adrenals. In blast crisis, the infiltrate consisted of myeloblasts and mature cells, while in CGL without blast crisis, they were almost entirely of mature cells. The average duration of disease was significantly longer for CGL with blast crisis (41.3 months) than for CGL without blast crisis (29.4 months).

- 1343 CYTOPHOTOMETRIC STUDIES OF THE CARCINOGENIC ACTION OF LIGHT FROM RUBY LASERS. (Ger.)

Ehlers, G. (Dermatol. Clin., Technical U., Munich, Germany) and H. J. Florian. *Hautarzt* 24(10):423-428, 1973.

Shaved skin on the abdomens of 2-month-old male and female C57Bl mice was exposed to total doses of 1-32 joules/cm² light from a ruby laser (694.3 nm) or from a xenon flash lamp with a red filter. Gross examination showed that hair growth was first stimulated and then inhibited and hair lost its pigmentation after exposure to both types of radiation. Histological examination of the skin revealed, independent of the total dose, many pyknotic nuclei, degenerative phenomena in the hair follicles and collagen fibers, and chronic inflammation in connective and fatty tissue. No signs of epidermal or follicular proliferation were detected in any of the mice. Cytophotometric determinations of DNA in epidermal cells showed the presence of DNA maxima in the hypodiploid, diploid, or hyperdiploid phases in mice of both groups. With the exception of three mice irradiated with total doses of 32 joules/cm² of light from the ruby laser or conventional light source, no statistically significant increases occurred in the mean DNA content or in the mean scattering. The increase in cells with a hypodiploid DNA content can be attributed to the increase in pyknotic nuclei in the area exposed to radiation. These findings cannot be interpreted as laser-specific. Long-term animal studies have not provided any evidence that radiation from the ruby laser is carcinogenic.

- 1344 NON-RADIATION EFFECTS OF THOROTRAST AND OTHER COLLOIDAL SUBSTANCES. (E.) Riedel, W. (Steglitz Clin, Free U., Berlin, Germany), B. Muller and A. Kaul. *Proc Third Intl Meeting Toxicity Thorotrast*: 281-293, April 1973.

The current literature on the pathogenetic effects of some nonradioactive colloidal substances in animals

reviewed. The effects of these substances suggest that the pathogenic effects of thorotrast are related to other than its radioactive properties. Preliminary plans for studying the role of the foreign body effect in the pathogenesis of thorotrast using experimental animals are presented. The animals would be exposed to Zr-95-labeled ZrO_2 , Hf-181-labeled HfO_2 (nonradioactive colloids possessing particles of sizes similar to those found in thorotrast), and Th-230-labeled thorotrast aerosols. Preparation of ZrO_2 aerosols using the peptization and condensation methods had failed to yield aerosols with the proper particle size distribution. Thorotrast has been produced following the method of the former manufacturer. To obtain alpha energy emission rates 100 times greater than those of commercial thorotrast, an activity ratio of 800 between Th-230 and Th-232 is required.

1345 FOLLOWUP OF THOROTRAST PATIENTS FROM BOSTON, MASSACHUSETTS AND ANN ARBOR, MICHIGAN, USA. (E.) Janower, M. L. (St. Vincent Hosp., Worcester, Mass.). *Proc Third Intl Meeting Toxicity Thorotrast*: 126-136, April 1973.

Over one hundred and twenty-four patients who received thorotrast for cerebral angiography and 315 control patients who underwent similar examinations without thorotrast injection were followed up to determine the incidence of radiation-related morbidity and mortality. Forty-two of the Thorotrast patients and 29 of the controls were subjected to extensive clinical and laboratory examinations. In the Thorotrast series, one case each of liver tumor, granulocytic leukemia, and nonalcoholic hepatic cirrhosis was found, and there were two cases of localized thorotrastomas. The Thorotrast patients showed evidence of early liver dysfunction as revealed by elevations in bromsulphalein retention and alkaline phosphatase tests. The most sensitive indicator of radiation exposure was the high frequency of chromosome aberrations. Anemia, elevated white counts, and abnormalities in red cell morphology were not found. Three possible cases of thorotrast attributable deaths (not in this series) were uncovered during the study; these included one case each of cholangiohepatoma, hepatoma, and aplastic anemia.

1346 ASPECTS OF COLLABORATION RELATING TO FOLLOW-UP-STUDIES. (E.) Immich, H. (Dept. of Documentation Statistics, U. Heidelberg, Germany). *Proc Third Intl Meeting Toxicity Thorotrast*: 317-320, April 1973.

It is felt that the thorotrast carrier group is dying out, and international collaboration is needed to get as much relevant information as possible from the study of this population. Both the investigative techniques and the data recording system must be the same internationally. It would also be desirable to develop a standardized basic program which would be as small as possible to lessen the influence of different physicians and different laboratory and radiological techniques. Since follow-up studies could not realistically

be carried out using one or more control groups, these studies should be carried out as cohort or profile studies. This would allow: testing of hypotheses using the respective data of the country in question only; the making of estimations based on the assumption that all elements of the sample are independent; and use of the life table method for determination of the survival time or duration until the first manifestation of malignancy. The aim of the studies will be to publish all original data, making only descriptive evaluations from it.

1347 THOROTRAST INJURY IN JAPAN. (E.) Mori, T. (Yokohama City U. Sch. Med., Japan), Y. Nozue, T. Miyazi and S. Takahashi. *Proc Third Intl Meeting Toxicity Thorotrast*: 175-192, April 1973.

Thorotrast was used clinically in Japan between 1928 and 1954, being used chiefly for the diagnosis of traumatic diseases in war-wounded servicemen since 1937. The first report of Thorotrast injury was hepatic cirrhosis in 1954; the first occurrence of hepatic cholangiocarcinoma following Thorotrast administration was reported in 1951. Between 1945 and 1970, autopsy findings from 94 Thorotrast-treated individuals (77 men) were examined. Thorotrast administration was considered a contributing factor to the cause of death in 91 cases; the incidence of malignancies, particularly hepatic tumors, was particularly high, as were the incidences of blood disease and liver and spleen fibrosis. A follow-up study was conducted using 147 war-wounded ex-servicemen to whom Thorotrast had been administered 31-36 years earlier. Six cases of malignant liver tumor, one case of leukemia, one case of thrombocytopenic purpura, and five cases of cirrhosis of the liver were found. The incidence of these diseases in the Thorotrast-treated individuals was significantly higher than in a control sample. Liver function tests on 45 of the Thorotrast group revealed a lowered protein metabolic rate and foreign body discharge function. Blood tests indicated decreased number of erythrocytes and leucocytes, decreased hemoglobin values, and decreased thrombocyte counts. Again, these findings were significant compared with those from a control group. The total number of Thorotrast-treated people living in Japan as of 1972 was estimated at 5,000.

1348 SPECIAL CLINICAL FINDINGS AMONG THOROTRAST PATIENTS. (E.) van Kaick, G. (Inst. Nuclear Med., German Cancer Res. Ctr., Heidelberg), D. Lorenz and I. Drings. *Proc Third Intl Meeting Toxicity Thorotrast*: 163-168, April 1973.

Among 800 patients who had been treated with Thorotrast, four liver tumors were found, along with one case of chronic myeloid leukemia and one case of an extended hemorrhagic pleural effusion. Nonneoplastic thorotrast-related diseases included numerous forms of hepatopathy ranging from fibrosis to cirrhosis of the liver. Long term sequelae caused by paravascular thorotrast deposits were frequently encountered. Since the liver is the most frequently injured organ in thorotrast patients, several diagnostic methods were combined to obtain a detailed diagnosis. The diagnostic

program consists of assays for alpha-1-fetoprotein, x-ray examinations of the upper abdomen, sonographic examinations, scintigram examinations, laparoscopy, and celiac arteriography. This program keeps patient stress within tolerable limits while providing satisfactory diagnostic results.

- 1349 ACTUAL STATUS OF THE GERMAN THOROTRAST STUDY.
(E.) van Kaick, G. (Inst. Nuclear Med., German Cancer Res. Ctr., Heidelberg) and K. E. Scheer.
Proc Third Intl Meeting Toxicity Thorotrast: 157-162, April 1973.

The German thorotrast study is a supra-regional "compound-research program" involving clinical and biophysical examinations of thorotrast patients and proper controls. To date, 6000 thorotrast patients and 6000 controls have been researched; about 80% of these have died. During the past 4 yr, 800 living thorotrast patients and 600 controls were studied, the cause of death being determined for those patients dying more than 3 yr after the injection of thorotrast. Patients and controls are examined using anamnesis, laboratory findings, x-ray examination of the abdomen, thorax, and site of injection, and evaluations of the general state of health. The cause of death has thus far been determined in 950 thorotrast patients and 800 controls. At the present time, the data indicate a higher incidence of liver tumors, liver cirrhosis, leukemias, and aplastic anemias among the thorotrast group. Several months ago, a follow-up study was begun which includes all patients who were examined more than 2 yr previously. The incidence of thorotrast-induced neoplasias appears to still be increasing.

- 1350 AEROSOL PARTICLES ON TOBACCO TRICHOMES.
(E.) Fleischer, R. L. (Atmospheric Physics Chem. Lab., Natl. Oceanic Atmospheric Admin., Boulder, Colo.) and F. P. Parungo. *Nature* 250(5462): 158-159, 1974.

Trichomes from North Carolina flue-cured and Turkish air-cured tobacco leaves were examined by X-ray spectrometry. Silicon, sodium, chlorine, calcium, and potassium were frequently seen, while iron and lead were found occasionally. Aerosol particles of greater than 0.5 μm diameter were attached to most of the trichome tips of the North Carolina tobacco and half of those of the Turkish tobacco. The North Carolina particles contained silicon and iron, while the Turkish particles contained chlorine. These compositions indicate that the particles were silicate minerals and salt, respectively. Trichome tips at positions where no exterior particles were visible showed silicon in half of the North Carolina samples, while other portions of the leaves showed none. Sodium and chlorine were found on the tips and stems of the Turkish samples, with silicon and lead being present in about half of the tips. These results support the hypothesis that radon daughter radioactivity precipitates on aerosols which diffuse to trichome tips and later become insoluble residues in tobacco smoke.

- 1351 CHROMOSOME ABERRATIONS CAUSED BY THOROTRAST.
(E.) Kemmer, W. (Boris Rajewsky Inst., U. Saarlandes, Homburg, Germany), H. Muth, F. Tranekjer and U. Borkenhagen. *Proc Third Intl Meeting Toxicity Thorotrast*: 104-113, April 1973.

Peripheral blood lymphocytes from 68 persons who had been injected with thorotrast between 1938 and 1947 were examined to determine whether a significant relationship exists between the rate of chromosome aberrations and the radiation dose. Chromosome aberrations were defined in terms of dicentrics and accompanying fragments. An increasing statistical correlation was found, which is representable by the straight line equation: $y = 6.6 + 0.16x$, where y is the aberration rate and x is the radiation dose. A computed curve for these values is represented by the power function: $y = 4.4x^{0.22}$. Although the two relationships are statistically significant (at the 1% and 5% levels, respectively), it is impossible to establish a dose-effect relationship between radiation dose and chromosome aberration rate in thorotrast patients because the number of dicentrics scatters within large limits in different patients exposed to equal or similar doses.

- 1352 THOROTRAST-INDUCED SPINDLE CELL SARCOMA AND HEPATIC CHOLANGIOCARCINOMA IN SYRIAN HAMSTERS.
(E.) Mori, T. (Second Dept. Path., Yokohama City U. Sch. Med., Japan), T. Okamoto, M. Umeda, K. Saito and H. Okazima. *Proc Third Intl Meeting Toxicity Thorotrast*: 267-290, April 1973.

Thorotrast (0.1, 0.2, 0.4 or 0.6 ml) was injected into the submucosal soft tissue of the cheek pouches of healthy Syrian hamsters. In a second experiment, thorotrast (1.0, 1.5, or 2.5 ml) was injected into the sublingual veins of Syrian hamsters. In the local experiment, 7 of 12 animals surviving more than 250 days developed spindle cell sarcomas at the site of injection. The time interval between thorotrast injection and macroscopic recognition of tumor formation ranged from 295 to 472 days, increasing levels of thorotrast producing shortened latency periods. The time interval between tumor recognition and death ranged from 33-48 days. The carcinogenesis of the tumors proceeded from thorotrast foreign body inflammation to thorotrastoma formation to spindle cell sarcoma development. About 6 months after injection, translocation of thorotrast granules to the liver, lung, and spleen began. In the systemic experiment, 9 cases of adenomatous proliferation in the liver and 3 cases of hepatic cholangiocarcinoma were found among the 15 animals surviving more than 150 days; the incidence of these diseases was dose related, as was the mortality rate and the latent period between thorotrast injection and hepatic cholangiocarcinoma appearance. The carcinogenesis of the hepatic cholangiocarcinomas proceeded from thorotrast deposition in the liver to adenomatous proliferation in the intrahepatic bile ducts to the development of hepatic cholangiocarcinoma. Systemic thorotrast administration also resulted in an abnormal proliferation of alveolar epithelial cells in the lung.

- 1353 CHRONIC WOUNDS CAN LEAD TO CANCER. (E.)
Wein, A. J. (No affiliation), W. P. Graham
III and H. P. Royster. *Int J Occ Health Safety* 43
(3):41-43, 1974.
- 1354 EPITHELIOMAS OF THE SCALP AFTER IRRADIATION.
(E.) Ridley, C. M. (Whittington Hosp.,
London, England) and M. F. Spittle. *Lancet* (7356):
509, 1974.
- 1355 RADIATION-INDUCED CARCINOMA OF THE RECTUM.
A LATE COMPLICATION OF PELVIC IRRADIATION.
(E.) Qizilbash, A. H. (Henderson Gen. Hosp., Ontario,
Canada). *Arch Pathol* 98(2):118-121, 1974.
- 1356 OESOPHAGEAL CANCER. (E.) Bhangoo, K. S.
(Mercy Hosp., Buffalo, N.Y.). *Lancet*
(7856):513, 1974.
- 1357 ACUTE LEUKEMIA FOLLOWING LOCALIZED IRRADIA-
TION FOR CARCINOMA OF THE LARYNX. (E.)
Karchmer, R. K. (Pub. Hlth. Serv., Ctr. Dis. Con-
trol, Bethesda, Md.), G. G. Caldwell and T. D. Y.
Chin. *Blood* 43(5):721-725, 1974.
- 1358 BURN SCAR CARCINOMA AND HYPERCALCEMIA.
(E.) Gerner, R. E. (Roswell Park Mem.
Inst., Buffalo, N.Y.) and G. E. Moore. *Ann Surg* 180
(1):95-97, 1974.
- 1359 SKIN CANCER CAUSED BY A RADIOACTIVE GOLD
RING. (Ger.) Holubar, K. (Dept. Micro-
biol., State U. New York, Buffalo), F. Helm and E.
Klein. *Hautarzt* 24(11):489-491, 1973.

See also:

- * (Rev): 1205, 1207
- * (Chem): 1319
- * (Viral): 1369
- * (Immun): 1476, 1493
- * (Epid-Biom): 1565, 1594

- 1360 EVIDENCE FOR A ROLE OF THE EPSTEIN-BARR VIRUS IN THE ETIOLOGY OF HUMAN LYMPHOMA. (E.) Levine, P. H. (Nat'l. Cancer Inst., Bethesda, Md.). *Biomedicine* 20(2):86-89, 1974.

A viral etiology for human lymphoma was first considered when epidemiological studies showed Burkitt's lymphoma had a geographic distribution overlying the malaria belt. The serological association of high antibody titers to Epstein-Barr virus (EBV) and the presence of Burkitt's lymphoma was then illustrated and studies to examine EBV-associated antigens, thus firmly establishing the link between EBV and Burkitt's lymphoma. Studies of Burkitt's lymphoma victims in non-malarial areas showed these patients had high EBV titers. Epidemiologic studies have also suggested that a transmitted virus might be responsible for Hodgkin's disease. A relation has been established between EBV and Hodgkin's disease and the titers were linked to both the histological subtype and prognosis. When serological tests to more than one herpes virus have been performed on the same area, the titers to herpes viruses other than EBV were not elevated, therefore indicating the specificity of the EBV associated antibody response. Additional indirect evidence relating EBV to Hodgkin's disease has been provided by epidemiological and pathological studies linking infectious mononucleosis to Hodgkin's disease. A study which linked an infectious mononucleosis registry with a tumor registry showed that there was only one form of cancer that had a higher incidence subsequent to documented infectious mononucleosis than would be expected -- lymphoma. A proposed histological link between infectious mononucleosis, Burkitt's lymphoma, and Hodgkin's disease is provided by a report of Reed-Sternberg cells in lymph nodes from patients with these lymphoproliferative diseases. This detection of the Reed-Sternberg cell in other diseases with high EBV titers may be extremely important. Studies have suggested that an RNA virus may also be involved and that a herpes virus alone may not be able to produce a lymphoma without an RNA virus cofactor. It is also possible that the high EBV titers may be a marker of a specific defect associated with the cause of cancer but may not be the direct response to EBV as an oncogenic agent.

- 1361 CHOLINE PHOSPHOTRANSFERASE AND PHOSPHATIDYL ETHANOLAMINE METHYLTRANSFERASE ACTIVITIES IN SPLEEN MICROSOMES OF MICE INFECTED WITH FRIEND VIRUS. (E.) Skurdal, D. N. (U. North Dakota Med. Sch., Grand Forks), D. J. Rytter and W. E. Cornatzer. *Proc Soc Exp Biol Med* 146(3):844-848, 1974.

Male Sprague-Dawley and BALB/c mice were inoculated i.p. with a Friend leukemia virus preparation. After 5, 10, 14, and 21 days, the spleen microsomes of these animals were analyzed for the activity of choline phosphotransferase and phosphatidyl ethanolamine methyltransferase. Compared with control microsomes from noninfected mice, the activity of choline phosphotransferase was markedly stimulated in the spleen microsomes of the virus-infected animals; the peak activity was observed at 5 days. There was comparatively less stimulation of phosphatidyl ethanolamine methyltransferase. The spleens of the virus-infected

animals were 10 times heavier than the control spleens on day 5 and 17 times heavier on day 10. The incorporation of 1,2-¹⁴C-choline and 1,2-¹⁴C-ethanolamine into the total phospholipid-P, total lecithin-P, and phosphatidyl choline-P fractions of the spleen microsomes was studied 1, 2, and 3 hours after the i.p. injection of the isotopic compounds into mice infected with Friend virus 14 days earlier. Compared with the controls, the incorporation of 1,2-¹⁴C-choline into the total phospholipid-P, total lecithin-P, and phosphatidyl choline fractions was increased in the microsomes from the virus-infected animals. Friend virus greatly stimulates the activity of choline phosphotransferase, which catalyzes the reaction of CDP-choline- α,β -diglyceride to form phosphatidyl choline.

- 1362 METASTASIS AND GROWTH OF FRIEND TUMOR CELLS IN IRRADIATED SYNGENEIC HOSTS. (E.)

Matioli, G. (U. Southern California Sch. Med., Los Angeles). *J Reticuloendothel Soc* 15(4):282-296, 1974.

The kinetic behavior of Friend tumor cells (FTC) growing in lethally irradiated syngeneic DBA/2J mice was studied. After establishing the FTC dilution factor (δ), extinction factor (Q), and the optimal time for colony counts, the FTC growth kinetics were analyzed by the recovery curve method. The growth of FTC differed from that of normal and leukemic Friend stem cells tested using the same *in vivo* assay. The FTC showed a higher metastatic activity, a lack of differentiation, deterministic growth, and independence from the spleen microenvironment. The primary FTC colonies grow to a minimum of 12 to 13 cells before metastatic processes commence. Most of the metastatic FTC appear to colonize the spleen through the peripheral circulation.

- 1363 SUSCEPTIBILITY AND RESISTANCE TO FRIEND LEUKEMIA VIRUS: EFFECT ON PRODUCTION OF MIGRATION-INHIBITION FACTOR. (E.) Mortensen, R. F. (Dept. Microbiol., Pennsylvania State U., University Park), W. S. Ceglowski and H. Friedman. *J Nat'l Cancer Inst* 52(2):499-505, 1974.

Infection of leukemia-susceptible DBA/2 and BALB/c mice with Friend leukemia virus (FLV, 50 ID50) depressed the cell-mediated immune function of delayed hypersensitivity and its *in vitro* correlate, the production of macrophage migration-inhibition factor (MIF). Significant immunosuppression, as measured by the ability of spleen lymphocytes to produce MIF, was detected as early as three days postinfection. Susceptible mice vaccinated with formaldehyde-inactivated FLV were resistant to the depression of delayed hypersensitivity or MIF production and to Friend disease. The responsiveness of adherent spleen cells from leukemic mice to MIF-rich culture supernatants was not impaired; however, the nonadherent spleen lymphocytes could not generate MIF. Although DBA/2 and BALB/c mice have different *FV-1* genotypes, both strains were susceptible to the NB-tropic FLV, and both displayed similar patterns of depression of established delayed hypersensitivity. In contrast, cellular immunity of the

absolutely resistant C57BL/6 strain was unaltered by FLV infection. These observations suggest an immunologic basis for the genetic resistance to murine leukemia viruses.

1364 STUDIES ON TARGET CELLS OF FRIEND SPLEEN FOCUS-FORMING VIRUS IN MICE. (E.)

Thomson, S. (Dept. Microbiol., Mahidol U. Bangkok, Thailand), P. Srivantanakul and E. A. Mirand). *Proc Soc Exp Biol Med* 145(4):1329-1332, 1974.

The nature of the target cells of Friend spleen focus-forming virus (SFFV) for virus replication and cell transformation was investigated. Growth of SFFV, SFFV-induced tumor cells, and certain hemopoietic cells was studied in mice that received different treatments to alter their population of hemopoietic cells. Inbred C3H/HeJ, C57BL/6J x C3H/HeJ (B6C3F₁) and its reciprocal, hybrid, and random-bred Swiss mice were used. Destruction of hemopoietic cells by irradiation or by myleran caused a great reduction in the susceptibility of mice to SFFV infection. Such mice became more susceptible to SFFV when more hemopoietic cells were made available through an infusion of bone marrow cells. Normal colony-forming cells as well as other hemopoietic cells were stimulated to proliferate in these mice. Thus a change in the susceptibility to SFFV in the treated mice probably resulted from an alteration in the number of target cells for SFFV. In studying the growth kinetics of SFFV, SFFV-induced tumor cells, and normal colony-forming cells, it was concluded that the increase in the virus and tumor cells should be directly proportional to the increase in the target cells. It is noted that, at 12 and 15 days after myleran treatment, normal colony-forming cells were the target cells. Neither is it likely that bone marrow myelocytes and blood neutrophils were target cells. It is suggested that cells in the erythrocytic pathway, probably erythropoietin-sensitive cells, may be involved in SFFV replication and in SFFV induction of tumor cells.

1365 BREAKDOWN OF GROSS VIRUS-INDUCED TOLERANCE IN RATS BY INOCULATION OF LYMPHOID CELLS.

(E.) Takeichi, N. (Hokkaido U. Sch. Med., Sapporo, Japan), N. Kuzumaki, T. Kodama and H. Kobayashi. *J Natl Cancer Inst* 52(6):1817-1822, 1974.

The i.p. inoculation, in Wistar King Aptekman/MK rats, of spleen and lymph node cells or thymus cells from syngeneic immune donors destroyed tolerance induced by Gross virus (GV). When tolerance was abrogated, the rats produced the cytotoxic antibody and resisted transplantation to GV-induced tumor (WGT-4) cells; none developed primary thymomas. The cytotoxicity test proved that the cells acquiring GV-specific cell-surface antigen were in the thymus of tolerant rats and disappeared after inoculation of immune cells. Histologically, thymus atrophy with depleted lymphocytes and enlarged spleen with proliferating reticular cells were observed 12-15 days after immune cell inoculation. These lesions disappeared completely by the 21st day. The mechanism of abrogating tolerance

is considered the immunologic interaction between inoculated cells and those acquiring a new cellular antigen in the host.

1366 RESTRICTION OF HERPES SIMPLEX VIRUS TYPE 1 REPLICATION IN ONCORNAVIRUS-TRANSFORMED

CELLS. (E.) Campbell, W. F. (Life Sci. Inst., St. Petersburg, Fla.), B. K. Murray, N. Biswal and M. Benyesh-Melnick. *J Natl Cancer Inst* 52(3):757-761, 1974.

Plaque formation and the growth characteristics of herpes simplex virus type 1 (HSV-1) were studied in: rat cells transformed by either murine sarcoma-leukemia virus (MSV-MLV) or by Rous sarcoma virus (RSV); rat cells infected with MLV only; baboon cells transformed by feline sarcoma virus (FeSV); and mouse cells (BALB/3T3) transformed by MSV. Both plaque formation and the replication of HSV-1 were markedly or totally inhibited in cells transformed by RSV, FeSV, MSV, and MSV-MLV, whereas they were only slightly restricted in cells infected with MLV. DNA synthesis was also inhibited in the cell lines which failed to support HSV-1 production. The inhibition or restriction of HSV-1 biosynthesis in the transformed cells appeared to be an intracellular phenomenon.

1367 ERRONEOUS INTERPRETATION OF VALID EXPERIMENTAL OBSERVATIONS THROUGH INTERFERENCE BY THE LDH VIRUS. (E.) Riley, V. (Pacific Northwest Res. Fdn., Seattle, Washington). *J Natl Cancer Inst* 52(6):1673-1676, 1974.

Many authors, using mice as experimental tools, have confused various experimentally observed tumor behavior, immunologic phenomena, and irregular therapeutic efficacies with the superimposed influences of the ubiquitous lactate dehydrogenase (LDH) virus. This inconspicuous, persisting, benign murine virus, which has been found in over 100 varieties and strains of mouse tumors, has potent capabilities for altering various fundamental host physiologic properties which, in turn, modify both neoplastic processes and the therapeutic effects of enzymes on tumors in mice. The LDH virus produces striking decreases in the clearance capacities of the mouse for eliminating certain exogenous enzymes, this and numerous other LDH virus-induced effects being dependent on the duration of residence of the virus in the host. The LDH virus also alters the immunologic competence of the host, has a lytic action on the thymus and T-cells, and has a stimulating influence on the spleen and lymph nodes. Thus, the findings of many authors working with mouse tumors, leukemias, and oncogenic viruses may be due to or influenced by the unknown or ignored presence of the LDH, or possibly other infectious contaminants. These authors should have their mouse tumors, leukemias, and oncogenic virus preparations examined for the presence or absence of the LDH virus. If the virus is present, it can usually be removed by cell-culture or heterotransplantation techniques.

1368 ASSOCIATION BETWEEN HERPES HOMINIS TYPE 2
AND THE MALE GENITOURINARY TRACT. (E.)

Deardourff, S. L. (U. Florida Coll. Med., Gainesville),
F. A. Deture, D. M. Drylie, Y. Centifano and H. Kauf-
man. *J Urol* 112(1):126-127, 1974.

Specimens, including urethral swabs, prostatic fluid, vas deferens sections, foreskins and testicular and prostatic biopsies were collected from 273 patients, aged 15 to 85 yr, from mixed racial and socioeconomic composition. From these 273 men, 40 positive cultures for herpesvirus type 2 were obtained. Prostatic fluid, vas deferens sections and prostatic biopsy specimens showed the highest percentages of positives and had a 2 to 4 times higher recovery rate than urethral swabs. This study indicated that herpes virus is present in the male genitourinary tract, especially in deeper tissues. It is suggested that viruses could persist in a dynamic state with latent infection maintained by constant replication of infectious virus in cells. By contrast, a static state could exist with the virus maintained in a non-replicating state for long periods and then reactivated. Theoretically, the ultimate latency would be integration of virus particles into cellular chromosomes with subsequent genetic transmission.

1369 ULTRAVIOLET-ENHANCED REACTIVATION OF HERPES
VIRUS IN HUMAN TUMOR CELLS. (E.) Lytle, C.

D. (Food Drug Admin., Rockville, Md.), S. G. Benane and L. E. Bockstahler. *Photochem Photobiol* 20(2):91-94, 1974.

The ultraviolet reactivation (UVR) effect, which is the enhancement of infectivity of UV-irradiated virus following UV-irradiation of the host cell, was studied using Herpes simplex virus and normal (embryonic lung) and malignant (HeLa) human cells. Although the lung cells displayed no UVR, both the HeLa cells and a Sendai-virus carrier culture of HeLa cells demonstrated UVR capabilities. This UVR persisted at equal or increased levels for at least 24 hr. Since the lung cells and HeLa cells have similar host-cell-reactivation (HCR) abilities, the differences in UVR capabilities suggest the UVR and HCR may operate by different mechanisms.

1370 GENITAL HERPES IN GUINEA-PIGS: AN EXPERI-
MENTAL MODEL WITH HERPESVIRUS HOMINIS.

(E.) Lukas, B. (Res. Dept., Pharmaceuticals Div., Ciba-Geigy, Ltd., Basel, Switzerland), W. Wiesen-
dang and K. H. Schmidt-Ruppin. *Arch Gesamte Virus-
forsch* 44(2):153-155, 1974.

Male and female guinea pigs, rabbits, and beagles and estradiol-progesterone primed juvenile female rabbits, rats, and mice were inoculated with herpesvirus hominis type 2 (HVH2)/Angelotti grown in HeLa cell culture. None of the male animals showed any symptoms of genital infection, while the female beagles and unprimed rabbits showed slight, transient local symptoms. Thirty percent of the mice developed encephal-

itis. Clearly positive symptoms were obtained in the female guinea pigs, the albino animals being more sensitive to infection than the colored animals. Symptoms in the guinea pigs included vaginal secretion, vulvovaginitis, and vesiculation on the labia, introitus, and lower part of the vagina. This was followed by extension of the lesions, ulceration, and the formation of necroses. Thereafter, the lesions healed spontaneously or the process spread, culminating in paralysis of the hind legs or death (8th-20th day). Evidence for the causal involvement of HVH was obtained. This model appears to offer possibilities for the study of infectious and oncogenic mechanisms and experimental therapeutic studies in genital herpes.

1371 REGRESSION OF AUTOCHTHONOUS MOLONEY SAR-
COMA VIRUS-INDUCED TUMORS IN MICE TREATED
WITH POLYRIBOINOSINIC ACID-POLYRIBOCYTIDYLIC ACID.
(E.) De Clercq, E. (Rega Inst. Med. Res., U. Leuven,
Belgium) and W. W. Stewart, II. *J Natl Cancer Inst*
52(2):591-594, 1974.

NMRI mice infected neonatally with the Moloney strain of murine sarcoma virus (M-MSV, 0.05 ml of $10^{-2.6}$ dilution i.m.) developed progressively and growing tumors. These tumors did not regress and invariably killed the host. However, if these animals were treated repeatedly with polyriboinosinic-polyribocytidylic acid (poly I:C, 200 µg i.p.) on alternate days (from 40 to 60 days after M-MSV inoculation), 75% of the established tumors regressed. The exact mechanism of this marked stimulatory effect of poly I:C on tumor regression is not known.

1372 BALB/cfRIII: A NEW HIGH MAMMARY-TUMOR AND
HIGH LEUKEMIA MOUSE STRAIN. (E.) Squartin
F. (Med. Sch., U. Pisa, Italy), G. B. Bolis and G.
Rossi. *J Natl Cancer Inst* 52(5):1635-1641, 1974.

A new inbred strain was established from a litter of BALB/c mice foster-nursed by RIII. This strain, BALB/cfRIII, carried the mammary tumor virus, received through RIII milk, and a leukemia virus. Accordingly BALB/cfRIII mice showed a high incidence of mammary tumors and lymphatic leukemia. During the first 30 generations of inbreeding, 1292 BALB/cfRIII mice were observed: 463 males, 723 breeding females (573 normally bred and 150 force-bred), and 106 virgin females. The pattern of spontaneous tumorigenesis was as follows: mammary tumors: 18.9% at 571 days of age in virgin females, 75.2% at 324 days in normally bred females, and 85.3% at 237 days in force-bred females; lymphatic leukemia: 43.6% at 380 days in males, 58.5% at 446 days in virgin females, 15.9% at 343 days in normally bred females, and 13.3% at 282 days in force-bred females. Lung tumors (3%) and ovarian tumors were sporadically observed in old mice. Association between mammary tumors and leukemia was rare. Most mammary tumors were pregnancy dependent. These data are compared with those of the strain of origin BALB/c and the milk-donor strain RIII.

1373 SUPPRESSION OF *IN VITRO* LYMPHOCYTE STIMULATION IN MICE BEARING PRIMARY MOLONEY SARCOMA VIRUS-INDUCED TUMORS. (E.) Kirchner, H. (Nat'l. Cancer Inst., Bethesda, Md.), R. B. Herberman, M. Glaser and D. H. Lavrin. *Cell Immunol* 13(1):32-40, 1974.

A marked depression of phytohemagglutinin (PHA) reactivity was observed in spleen cell cultures from C57BL/6N mice bearing primary Moloney sarcoma virus (MSV)-induced tumors. This defect was most pronounced 14 days after virus inoculation (MSV 14) and was reversed after regression of the tumor. Spleen cells from mice with primary methylcholanthrene-induced sarcomas were similarly deficient, while no such effect was observed during the first weeks after inoculation of Moloney leukemia virus. The responses of MSV 14 spleen cells to Concanavalin A (Con A) were as consistently depressed as those to PHA, but reactivity to bacterial lipopolysaccharide was affected to a lesser degree. Stimulation by pokeweed mitogen (PWM) was not significantly reduced in tumor-bearing mice compared with control animals. Passage of MSV 14 spleen cells over rayon adherence columns which removed about 75% of the initial cell population led to an almost complete restoration of their PHA and Con A responses on a per cell basis. This may indicate that within MSV 14 spleens, T lymphocytes reactive to PHA and Con A are diluted out by a majority of unreactive cells. However, the possibility also exists that column passage removes a suppressor cell that actively inhibits these responses.

1374 TRANSMISSION OF THE MAMMARY TUMOR VIRUS BY THE GR MOUSE STRAIN. II. GENETIC STUDIES. (E.) Nandi, S. (Cancer Res. Lab., U. California, Berkeley) and C. Helmich. *J Natl Cancer Inst* 52(5):1567-1570, 1974.

The genetic basis of congenital transmission of mammary tumor virus (MTV) by GR females was studied with F_1 , F_2 , and backcross populations of GR X BALB/c (C^-) mice. All mice were foster-nursed by MTV-free C^- mothers. The occurrence of one or more of the three kinds of mammary lesions (pregnancy-dependent tumors, pregnancy-independent tumors, or hyperplastic nodules) in force-bred females within the first yr was considered an indication of MTV infection. A mouse without mammary lesions was still considered MTV-infected if she transmitted MTV through her milk. Of reciprocal F_1 hybrids 100% developed mammary tumors by 7 months, and the incidence of mammary tumors in (GR X C^-) X GR backcrosses was also close to 100%. From the criteria used to determine MTV infection, 75% of the (GR X C^-) X C^- backcross females were MTV-infected. Although mammary lesions were detected in only 77% of the F_2 :[(GR X C^-) X (GR X C^-)] populations, some lesion-free mice also transmitted MTV by milk. It was predicted that at least 90% of the F_2 females were likely to be infected with MTV. The ratios of MTV-infected females in F_1 , F_2 , and backcross populations appeared compatible with the hypothesis that two independently segregating dominant genes in the GR mouse strain are involved in congenital transmission of its MTV, and that either one of these genes alone is adequate for MTV transmission.

1375 MECHANISM OF RESISTANCE TO MAMMARY TUMOR DEVELOPMENT IN C57BL AND I STRAINS OF MICE. II. INHERENT DIFFERENCES BETWEEN THE TWO STRAINS. (E.) Nandi, S. (Cancer Res. Lab., U. California, Berkeley). *J Natl Cancer Inst* 52(6):1797-1804, 1974.

Experiments were designed to follow the fate of mammary tumor virus (MTV) and host reactions to MTV and associated antigens in C57BL/Crg1 (C57) and I/Crg1 (I) mice. Introduction of C3H MTV into C57 and I mice, by transplantation of B-particle containing hyperplastic nodular outgrowth, resulted only in occasional milk transmission of MTV by these mice. However, (C57 X I) F_1 (F_1) mice, exposed to MTV, could transmit virus serially in successive passages. After natural (foster-nursing) or artificial (inoculation or transplantation) introduction into C57, I, and F_1 mice, MTV quickly disappeared in all three groups; thereafter, it remained undetectable in blood cells and hematopoietic tissues of C57 mice. MTV activity, however, reappeared rarely in blood cells and spleens of young I mice; such reappearance was always observed in blood cells of F_1 mice beginning at about 3-4 wk of age. Production of blood cell-associated MTV and noduligenesis failed to occur, even under strong hormonal stimulation, in C57 mice implanted with C57 mammary nodular outgrowths capable of continuous production of MTV B particles. Noduligenesis did occur in F_1 mice implanted with the same C57 nodular outgrowths. Transplanted I nodule outgrowths usually failed to establish or induce nodules in I hosts. After natural infection with MTV or after immunization with MTV-containing antigens, I, but not C57, mice developed virus-neutralizing antibodies. Few of the I nodules, when transplanted into untreated I host, survived and produced hyperactive outgrowths. However, a higher percentage of I nodules, when transplanted into I hosts treated with rabbit antimouse thymocyte serum, could produce hyperactive outgrowths. These results suggest that resistance of C57 mice to C3H virus-induced mammary tumorigenesis is due to the failure of the virus to cause adequate infection of hematopoietic cells, where nucleated blood cell-associated MTV is produced. The resistance of I mice to mammary tumorigenesis is probably due to their genetically determined high immunologic competence against MTV and associated antigens.

1376 TITRATIONS OF VARIOUS MOUSE MAMMARY TUMOR VIRUSES IN DIFFERENT MOUSE STRAINS. (E.) Moore, D. H. (Inst. Med. Res., Camden, N.J.), J. Charney and J. A. Holben. *J Natl Cancer Inst* 52(6):1757-1761, 1974.

Milks from the high-mammary-tumor mouse strains A, BALB/cfc3H, RIII, and C3H were titrated for infectivity in low-mammary-tumor strains C57BL, BALB/c, Af, and RIIf. 1) There was a wide variation in susceptibility of different mouse strains to the same virus; 2) the susceptibility of each mouse strain depended on the donor virus; i.e., mice resistant to mammary tumor virus from one strain were susceptible to virus from another strain; 3) RIIf mice were relatively resistant to the virus from the parent isogenic RIII strain; 4) infectivity maxima of milks ranged from dilutions of 10^{-3} to

10⁻⁶. In another experiment, C57BL, BALB/c, Af, and RIIIf mice were inoculated with pooled RIII milk and observed for 26 months to record tumor incidence. Incidence ranged from 0% in C57BL to 97% in BALB/c mice.

- 1377 HIGH-VIRULENCE MAREK'S DISEASE VIRUS INFECTION IN CHICKENS PREVIOUSLY INFECTED WITH LOW-VIRULENCE VIRUS. (E.) Smith, M. W. (Connaught Lab., Willowdale, Ontario, Canada) and B. W. Calnek. *J Natl Cancer Inst* 52(5):1595-1603, 1974

The pathogenicity of high-virulence (JM-10 isolate) Marek's disease virus (MDV) was compared in White Leghorn chickens with and without prior infection with a naturally low-virulence MDV isolate (CU-2) or the avirulent FC126 strain of turkey herpesvirus (HVT-4). Infection with CU-2 (360 focus-forming U) protected against JM-10 challenge (125 focus-forming U). Route of infection (intra-abdominal inoculation or indirect challenge) of CU-2 was not a factor in protectivity. CU-2 infection was not protective against simultaneous challenge with JM-10, but only 2 days' prechallenge time with CU-2 infection conferred maximal protection in susceptible birds. One-day-old chickens were no more susceptible than those 4-wk-old to CU-2 infection, but the younger CU-2-infected birds were not protected against JM-10 challenge. Bursectomy at hatching time had two effects. It increased the incidence of MD with either CU-2 or JM-10 infection (statistically significant only with the latter). Also, it altered the lesion spectrum in CU-2-infected chickens that developed MD; visceral tumors occurred in bursectomized birds, but only neural lesions were seen in intact birds. There was less viral antigen in lymphoid organs, and degenerative lesions were prevented in JM-10-challenged birds with prior CU-2 or HVT-4 infection. Cell-associated infectivity (both HVT-4 and JM-10) was present in spleen cells of those inoculated with both viruses, and the level of JM-10 infectivity was similar to that of chickens receiving only JM-10.

- 1378 AN ATTENUATED MOUSE LEUKEMIA VIRUS. I. ORIGIN AND IMMUNIZATION. (E.) Kirsten, W. H. (Joseph P. Kennedy, Jr., Mental Retardation Res. Ctr., U. Chicago, Ill.), E. Stefanski and S. Panem. *J Natl Cancer Inst* 52(3):983-985, 1974.

An attenuated Kirsten murine leukemia virus was isolated from the culture fluids of a chronically infected C3Hf/Gs mouse embryo cell line. The attenuated virus failed to induce erythroblastosis or thymic lymphomas in C3Hf/Gs, DBA/cJ, or BALB/cJ mice after 16-18 months. Inoculation of 3-wk-old C3Hf/Gs mice with attenuated leukemia virus prevented the induction of erythroblastosis and lymphomas by virulent virus administered 1 month later. A similar protective effect was observed when 3-wk-old Wistar/Furth rats were inoculated with attenuated virus and challenged 1 month later with a lethal dose of rat-adapted leukemia virus. This is the first indication that an attenuated murine leukemia virus grown in mouse cells can be used to immunize rats

against lymphoma induction by homologous, rat-adapted murine leukemia virus.

- 1379 EXPRESSION OF THE DEFECTIVE "S+L-" TYPE MURINE SARCOMA VIRUS GENOME IN HUMAN AMNION AND LUNG CELLS. (E.) Papageorge, A. G. (Natl. Inst. Allergy Infect. Dis., Bethesda, Md.), P. T. Peebles, B. I. Gerwin, P. J. Fischinger and C. F. T. Mattern. *J Natl Cancer Inst* 52(6):1727-1737, 1974.

Murine sarcoma virus (MSV) rescued from cloned sarcoma-positive leukemia-negative (S+L-) mouse cells was used to obtain a single cell clone, S+L-HuAC1₁, from a single-hit terminal focus in human AV-3 amnion cells. Second generation MSV, rescued from S+L-HuAC1₁ cells by superinfection with RD-114 virus, was used to generate three clones of S+L- cells derived from three separate MSV foci in L-132 human lung cells. S+L-human amnion and lung cell clones demonstrated certain characteristics of S+L- mouse cells: All 4 S+L- human cell clones were transformed, expressed the genetically stable murine leukemia virus group-specific antigen marker, and contained cryptic MSV rescuable by superinfection with compatible helper-type viruses that conferred host range properties on the rescued MSV pseudotypes. S+L- human cells differed from S+L- mouse cells in that the human cells did not release detectable C-type virus-like particles. S+L- human cells also lacked detectable quantities of the viral core protein reverse transcriptase. Although similar to nonproducer Kirsten-MSV transformed mouse cells, S+L- human cells failed to release detectable MSV after iododeoxyuridine induction.

- 1380 CHARACTERISTICS OF MURINE C-TYPE VIRUSES. II. THE BEHAVIOR OF VIRUSES RESIDENT IN VARIOUS CELL LINES AND THEIR HYBRIDS ON BALB/3T3 AND MOUSE EMBRYO FIBROBLAST CULTURES. (E.) Fenyo, E. M. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), K. Nazerian and E. Klein. *Virology* 59(2):574-579, 1974.

A quantitative focus test was established in mouse embryo fibroblast cultures for the detection of L virus present in an 8-azaguanine resistant subline (A9) of L cells. The titers obtained were 100-fold higher in N-type than in B-type cells, indicating that the L virus is N-tropic. The replication of viruses produced by two Moloney lymphoma sublines (Y and Yr), the A9 derivative (L), and their hybrids (YL and YrL) was studied in BALB/3T3 cells over a 6-day period. The Y, Yr, and YrL viruses were detectable by the XC plaque test, and the L and YL viruses were detectable by focus formation. On passage in BALB/3T3 cells, the original characteristics of these viruses in the two assay systems was retained. The outcome of studies involving infection on mouse embryo fibroblasts was similar. The viruses produced by the hybrid cells differed from the viruses resident in each parental cell entering the hybrids: the virus from YL hybrid was similar to the L virus in that it induced "early" foci in the mouse embryo fibroblasts, but it was NB tropic like the virus from the Y parent and, with high virus concen-

trations, XC plaque could sometimes be observed; unlike either parent, the virus from the YrL hybrid was focus negative, and it was plaque positive like the virus from the Yr parent, but N-tropic like the virus from the A9 parent. These data indicate that the properties of viruses are fixed in the cell.

- 1381 MUTANT OF POLYOMA VIRUS WITH IMPAIRED ADSORPTION TO BHK CELLS. (E.) Basilico, C. (New York U. Sch. Med., N.Y.) and G. DiMayorca. *J Virol* 13(4):931-934, 1974.

PY235 was isolated as a temperature-sensitive (TS) mutant from large-plaque (LP) polyoma virus (PY). Although PY235 is somewhat TS in plaque formation, it showed no TS in terms of growth; the yield was reduced at any temperature to about 1/10 that of wild type (WT)-infected cells. PY235 caused no detectable transformation of BHK-21 cells or rat ReCL3 cells. Thus, PY235 appeared to have a late defect. PY235 was unable to cause any significant hemagglutination (HA) when tested with guinea pig red blood cells (RBC); this was due to a lack of adsorption of the virus to RBC. The adsorption of ³H-labeled WT and PY235 virus to 3T3 and BHK cells was tested. Adsorption to the mouse cells was slow and inhibited to about 40% of WT values; adsorption to BHK cells reached only 5% of the WT values. These altered adsorption properties are responsible for the apparent inability of PY235 to cause cell transformation or hemagglutination.

- 1382 PATHOLOGICAL DYNAMICS OF PROLIFERATIVE PROCESSES IN THE SPLEEN OF NMRI MICE DURING THE EARLY PHASE OF RAUSCHER'S LEUKEMIA. (Ger.) Komitowski, D. (German Cancer Res. Ctr., Heidelberg) and K. Goerttler. *Exp Pathol (Jena)* 9(3):182-190, 1974.

Histological, histochemical, and autoradiographic studies were performed on spleens from 200 female NMRI mice which had been inoculated i.p. with cell-free supernatant of a spleen homogenate from mice with Rauscher's leukemia at age 8-10 wk. Animals were sacrificed 1-70 days after inoculation. Proliferative processes occurring in the red pulp were accompanied by characteristic changes in the white pulp. By 3 days after inoculation a decrease had occurred in the number of lymphocytes in the thymus-dependent area of the lymph follicles. This was associated with an enlargement in the germinal centers which became fully manifested on day 5. Tissue disorganization, which was evident on day 10, was followed by regeneration after day 30. By day 70, enlarged germinal centers in the regenerated lymph follicles had returned to their normal size. Histochemical investigations were performed by staining for alkaline phosphatase, 5-nucleotidase and nonspecific esterases. In leukemic mice cells with positive reactions for 5-nucleotidase and nonspecific esterases gradually became more homogeneously distributed throughout the entire spleen. While only the periphery of lymph follicles were positive for alkaline phosphatase in controls, the positive zone in leukemic mice rapidly increased in size until, by day 7,

all of the follicle was stained homogeneously. Autoradiographic studies performed after i.p. injection of ³H-thymidine revealed that an increase in labeled cells occurred in the lymph follicles by day 3. This increase was most pronounced in cells of the mantle. In addition, cells located near arteries were labeled. When the normal cell population in the spleen became flooded with leukemic cells it was no longer possible to determine which cells were being labeled. It is postulated that the histological changes observed in mice during the early phase of Rauscher's leukemia result from hematopoietic and immunological processes which occur simultaneously.

- 1383 AVIAN RHABDOMYOSARCOMAS INDUCED BY ROUS SARCOMA VIRUS. (E.) Levenbuk, I. S. (Tarashevich Sci. Res. Inst. Standardization Control Med. Biol. Preparations, Moscow, USSR), O. L. Kolomiyets, M. S. Vorobyeva, L. N. Guseva and E. S. Voronin. *Neoplasma* 21(1):21-28, 1974.

One ml of Rous sarcoma virus (RSV)-induced cell-free chicken tumor filtrate was injected into the wing web of 23 2-wk-old white Leghorn chickens and 48 1-month-old Japanese quails. Tumors appeared at the site of inoculation beginning 7 days after inoculation in the chickens and 5 days after inoculation in the quails. The tumors of both species were essentially of the same appearance, regardless of which strain of RSV was used to induce them. The histological and cytological features of the tumors, as shown by light microscopy, appeared to be rhabdomyosarcomas, particularly resembling those of the embryonal type. Although no transversally striped myoblasts were observed, this is not in contradiction to the diagnosis of rhabdomyosarcoma since the tumors were very poorly differentiated. Similarly, the low degree of differentiation can explain the absence of such structural signs of muscular differentiation as cross striations. In the quails, the rhabdomyosarcomas showed an immunomorphological reaction and showed a tendency to regress.

- 1384 POTENTIATION OF RSV RESCUE FROM RSV-TRANSFORMED "POORLY" VIROGENIC CELL LINES BY 5-BROMODEOXYURIDINE TREATMENT BEFORE FUSION WITH CHICK EMBRYO FIBROBLASTS. (E.) Donner, L. (Inst. Exp. Biol. Genetics, Czechoslovak Acad. Sci., Prague), H. Sainerova, J. Svoboda and S. Scherneck. *Int J Cancer* 13(1):37-42, 1974.

The ability of treatment with 5-bromodeoxyuridine (BUdR) and mitomycin C (MC) to potentiate the rescue of Rous sarcoma virus (RSV) from RSV-transformed "poorly" virogenic cell lines and to rescue the RSV from RSV-transformed nonvirogenic cell lines after fusion with chick fibroblasts was studied. The rescue of RSV from the poorly virogenic RSV-transformed rat lines LW13-RsK1 and LW13-RsK4 was achieved only after treatment with BUdR before fusion with chick embryo fibroblasts. Treatment of the RSV-transformed nonvirogenic mouse lines RVA4 and RVP3 with BUdR or MC before fusion with chick embryo fibroblasts did not lead to the production of RSV.

1385 HEMATOLOGICAL RESPONSES ASSOCIATED WITH RESISTANCE TO ROUS SARCOMAS IN FOUR STRAINS OF CHICKENS. (E.) Smith, J. L. (Dept. Animal Sci., U. Arkansas, Fayetteville), N. R. Gyles and L. T. Paterson. *Poult Sci* 53(3):1220-1230, 1974.

The leukocytic response to Rous sarcoma induction was studied in Arkansas Station Giant Jungle Fowl (JF) cockerels, White Leghorne (WL) cockerels, the F₁ hybrids resulting from the mating of JF males to WL females (F₁), and cockerels from a line selected solely for regression of Rous sarcomas (R x R). Hematological data were collected prior to Rous sarcoma virus (RSV) inoculation and then once weekly for 5 wk after challenge. The tumor responses varied in accordance with the respective genetic resistance of each breed; JF and R x R showed resistance, WL birds were generally susceptible, and the F₁ hybrids were intermediate between the two parental strains. The total number of leukocytes, when averaged over all six sampling periods, was higher in the treated birds than in uninoculated birds from all breeding groups. The greatest leukocyte response in the resistant JF and R x R cockerels was observed during the third wk after challenge; this corresponded to the time of expected tumor emergence. This response was less marked in the F₁ hybrids and completely absent in the susceptible WL birds. The differential leukocyte counts indicated that the response of the JF birds was due to an increase in lymphocytes, while the responses of the R x R and F₁ cockerels were due to increases in both lymphocytes and heterophils. The results indicate that lymphocytes may have a primary role in tumor resistance, with heterophils playing a secondary role.

1386 SIMIAN VIRUS 40 IN A HUMAN CANCER. (E.) Soriano, F. (Res. Education Div., Hlth. Cent. Inc. Life Sci. Fdn., Minneapolis, Minn.), C. E. Shelburne and M. Gökçen. *Nature* 249(5456):421-424, 1974.

A 70-yr-old plumber was found to have a malignant melanoma on the upper back which, at autopsy 3 yr later, had metastasized to the skin and muscles of the shoulder and chest wall, the lungs, pleuras, diaphragm, liver, lymph nodes, dura, brain, and heart. A primary grivet (African green monkey) kidney culture inoculated with a lung metastasis specimen yielded simian virus 40 (SV40) within 40 days. From another lung metastasis, virus was recovered in three further successive attempts using the grivet kidney-derived BSC-1 cell line. In two other experiments, SV40 was isolated from liver and muscle metastases. In each case, isolation of the virus was preceded by signs of cytopathic effects characteristic of SV40. Inoculation of tumor pellets into less sensitive grivet kidney cell lines (CV-1, Vero) yielded no virus, and BSC-1 cultures remained negative after inoculation with cell-free tumor extracts. Electron microscopy of a brain metastasis yielded no virions. Mice and hamsters inoculated at birth with pellets of metastatic tissues and pleural tumor cells developed no meaningful diseases. In cross-naturalization tests, no significant differences were found

between the six virus isolates and two known SV40 strains. The isolates were designated Strain F (SF) of SV40. It is identical to other strains in its intrinsic properties, growth in cell cultures, cytopathic effects, cell-transforming efficiency, oncogenicity, and electron microscopic features. Inoculation of SF-transformed mouse or hamster cell cultures in the respective hosts resulted in malignant tumors. Tumors could be prevented in hamsters inoculated at birth with SV40 strain A2895 by injecting SF during the incubation period. Identity of the cellular T antigen induced by SV40 with the SF-induced T antigen was demonstrated by indirect immunofluorescence.

1387 DIFFERENT CHROMOSOME MORPHOLOGY OF DIPLOID AND ANEUPLOID MALIGNANT CELLS. (E.) Mitelman, F. (U. Hosp., Lund, Sweden). *J Natl Cancer Inst* 52(2):561-564, 1974.

The phenomenon of blurred *versus* distinct chromosome morphology and its relation to karyotype were studied in 63 primary, 20 metastatic, and 124 *in vivo* transplanted Rous rat sarcomas. All sarcomas were examined in direct preparations from the tumors. There was a striking difference between metaphases with normal and abnormal chromosome complements: Cells with a normal diploid karyotype had blurred chromosomes, whereas those with aneuploid karyotypes exhibited distinct outlines. Both cell types were malignant and the difference in chromosome morphology was related to the degree of malignancy. It is suggested that leukemic marrow, like the sarcomas, contains a mixture of cells of different degree of malignancy. The results might therefore be relevant to the question of cytogenetic evidence for leukemic remission.

1388 POSITIVE CONTROL OF TRANSFORMED PHENOTYPE IN HYBRIDS BETWEEN SV40-TRANSFORMED AND NORMAL HUMAN CELLS. (E.) Croce, C. M. (Wistar Inst. Anat. Biol., Philadelphia, Pa.) and H. Koprowski. *Science* 184(4143):1288-1289, 1974.

Somatic cell hybrids were produced between SV40-transformed Lesch-Nyhan fibroblasts, which are deficient in hypoxanthineguanine phosphoribosyltransferase (HGPRT) and display glucose-6-phosphate dehydrogenase A (G6PD-A) activity, and late-passage HGPRT-positive W138 human embryo fibroblasts, which display G6PD-B activity. The hybrid cells selected in hypoxanthine-aminopterin-thymidine (HAT) medium displayed human HGPRT activity and human G6PD-A and G6PD-B and heteropolymers of the two enzyme forms. Clones back-selected in 8-azaguanine displayed only G6PD-A activity. All clones examined were positive for SV40 T antigen, indicating that the human chromosome 7 carrying the SV40T antigen gene and SV40 genome is rarely, if ever, lost. All of the hybrid cell clones behaved as continuous cell lines, and all were very close to tetraploidy. In addition, all clones had a plating efficiency and morphology similar to that of the SV40-transformed parental cells, and all piled up in culture and failed to display the properties of density-dependent inhibition of cell division.

- 1389 TRANSFORMATION ASSAY FOR MURINE SARCOMA VIRUSES USING A SIMIAN VIRUS 40-TRANSFORMED HUMAN CELL LINE. (E.) Todaro, G. J. (Nat'l. Cancer Inst., Bethesda, Md.) and C. A. Meyer. *J Natl Cancer Inst* 52(1):167-171, 1974.

A subclone derived from a simian virus 40 (SV40)-transformed human skin fibroblast culture (SV clone 80) was susceptible to focus formation by murine sarcoma viruses (MSV). Foci were transformed within 1 wk after infection and the transformed cells were isolated and serially propagated; they continued to contain SV40 T antigen and to produce both sarcoma virus and "helper" leukemia virus. MSV pseudotypes with mouse, woolly monkey, and gibbon type-C viruses all transformed SV clone 80 cells, whereas the "helper" type-C viruses themselves did not produce transformation. Interference of focus formation by preinfection with helper virus was demonstrated.

- 1390 ANTIGENIC PHENOTYPES AND COMPLEMENTATION GROUPS OF TEMPERATURE-SENSITIVE MUTANTS OF SIMIAN VIRUS 40. (E.) Robb, J. A. (Dept. Path., U. California, San Diego, La Jolla), P. Tegtmeier, A. Ishikawa and H. L. Ozer. *J Virol* 13(3):662-665, 1974.

The antigenic phenotypes of several temperature-sensitive-mutants of simian virus 40 were determined by an immunofluorescence microtechnique that allowed a very high degree of internal control for the conditions of virus infection and antigenic staining. The tumor (T), U, capsid protein (C), and virion (V) antigens were investigated. Productive infection in monkey TC7 cells and abortive infection in BALB/3T3 mouse cells were simultaneously monitored for antigen production at both permissive and restrictive temperatures. Complementation analyses of the mutants demonstrated two complementing groups (A and B) and one noncomplementing group. One of the complementing groups could be subdivided into two subgroups having very different antigenic phenotypes. The following phenotypes were observed at the restrictive temperature in monkey cells. (i) The noncomplementing group produced none of the antigens. (ii) Group A induced T antigen in moderately but consistently reduced numbers of cells. Other antigens were markedly reduced or absent. (iii) Some of the group B mutants produced T antigen but little or no U and V antigens. The C antigen appeared in the nucleolus and cytoplasm of this subgroup. (iv) In the other group B mutants, antigen synthesis was not altered. Similar phenotypes were observed in mouse cells, except that U, C, and V antigen could not be detected during either the mutant or wild-type virus infections at any temperature.

- 1391 DNA POLYMERASES IN HUMAN LYMPHOBLASTOID CELLS INFECTED WITH SIMIAN SARCOMA VIRUS. (E.) Lewis, B. J. (Nat'l. Cancer Inst., Bethesda, Md.), J. W. Abrell, R. G. Smith and R. C. Gallo. *Biochim Biophys Acta* 349(2):148-160, 1974.

A technique for isolating and separating DNA polymerases in mammalian cells infected with RNA tumor viruses is described. In whole cell extracts of

cultured human lymphoblastoid cells infected with simian sarcoma virus, four DNA polymerases were resolved, three of the enzymes being cellular and one being viral in origin. The viral reverse transcriptase and cellular DNA polymerase II were eluted from a DEAE-cellulose column at 50 mM KCl, while cellular DNA polymerases I and III (R-DNA polymerase) were removed at 0.3 M KCl. These DNA polymerase mixtures were then resolved on phosphocellulose and DNA-cellulose columns. The identities of the separate polymerases were further confirmed by primer template utilization, molecular size determination, and response to antibody to the viral enzyme. This procedure was designed for further application to the study of DNA polymerases in human leukemic cells and other human tumors. It may be necessary to use the subcellular-fractionation approach to isolate reverse transcriptase from nonvirus-producing cells, such as human leukemic cells, when the enzyme is present in small amounts.

- 1392 COMPARISON OF JC AND BK HUMAN PAPOVAVIRUSES WITH SIMIAN VIRUS 40: RESTRICTION ENDO-NUCLEASE DIGESTION AND GEL ELECTROPHORESIS OF RESULTANT FRAGMENTS. (E.) Osborn, J. E. (U. Wisconsin Med. Sch., Madison), S. M. Robertson, B. L. Padgett, G. M. Zu Rhein, D. L. Walker and B. Weisblum. *J Virol* 13(3):614-622, 1974.

JC virus, isolated from the brain of a patient with progressive multifocal leukoencephalopathy and propagated in human fetal glial cell cultures, had a buoyant density of 1.20 g/cm³ in linear sucrose-D₂O and 1.35 g/cm³ in cesium chloride isopycnic gradients. DNA extracted from JC-infected cultures or from gradient-purified virions occupied a dense position relative to linear DNA in cesium chloride/ethidium bromide gradients, and the circular configuration of the extracted DNA was confirmed by electron microscopy, with a measured molecular weight of 2.93 x 10⁶. DNA from BK virus was similarly prepared and compared with JC and with an SV40 DNA standard by digestion with restriction endonuclease preparations from *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Escherichia coli*. Digests were electrophoretically analyzed on gradient polyacrylamide slab gels or agarose gels, and the three viruses were found to have distinctly different cleavage patterns by this form of analysis: JC and BK viruses were almost entirely different from SV40 and significantly different from each other. Thus, JC and BK human papovaviruses appear to be discrete new members of the papovavirus group, rather than SV40 variants.

- 1393 FIBRINOLYSIS ASSOCIATED WITH ONCOGENIC TRANSFORMATION. MORPHOLOGICAL CORRELATES. (E.) Ossowski, L. (Rockefeller U., New York, N.Y.), J. P. Quigley and E. Reich. *J Biol Chem* 249(13):4312-4320, 1974.

The relationship between fibrinolysis and cellular morphology was studied using normal and Simian virus 40 (SV40)-transformed hamster embryo fibroblast cultures. The rate of fibrinolysis and the morphologi-

cal response were both influenced by the nature of the serum supplement; most sera showed an excellent correlation between the rate of fibrinolysis and the development of characteristic morphological changes. Both processes required the presence of the serum factor, plasminogen, and its conversion to plasmin. When normal and transformed fibroblasts were co-cultivated under appropriate conditions, the normal cells underwent morphological changes similar to those ordinarily expressed by transformed cells. The appearance of these changes in the normal cells was also correlated with the fibrinolytic activity and the activation of plasminogen. Fibrinolysis and morphological changes could be dissociated in media supplemented with bovine serum. When the macromolecular protease inhibitors were destroyed by acid treatment, the bovine sera became actively involved in fibrinolysis. However, they did not mediate morphological change and they contained a selective inhibitor of morphological transformation. Thus, an active fibrinolytic system is a necessary but not entirely sufficient requirement for the morphological changes accompanying transformation in hamster fibroblasts.

- 1394 INTEGRATION OF SV40 DNA AND INDUCTION OF CELLULAR DNA SYNTHESIS AFTER A *ts* SV40 INFECTION. (E.) Hirai, K. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), J. A. Robb and V. Defendi. *Virology* 59(1):266-274, 1974.

The early temperature-sensitive mutant of simian virus 40 (SV40), *ts*101*, was characterized in non-permissive Chinese hamster (ChH) and permissive monkey CV-1 cells for integration of viral DNA and induction of cellular DNA synthesis. At 42 C, this mutant did not induce the synthesis of T antigen, cellular DNA, or viral DNA in CV-1 cells. The viral DNA did not integrate into the CV-1 DNA, although nuclear penetration did occur. In the ChH cells, *ts*101* induced the synthesis of T antigen at 40 C and 42 C, and the viral DNA integrated into the ChH DNA; however, ChH DNA synthesis was not induced. These findings suggest that the integration of SV40 DNA does not depend on the replication of cellular DNA and that, at least functionally, integration precedes the induction of cellular DNA synthesis. The results also indicate that some function(s) related to the early phase of SV40 infection is regulated and/or provided by the host cell.

- 1395 FURTHER STUDIES ON SV40 PERMISSIVE CELL PROTEIN FACTOR(S) ALLOWING RESCUE OF INFECTIOUS VIRUS AND VIRAL DNA FROM NON-SHEDDER SV40-TRANSFORMED CELLS. (E.) Lavialle, C. (Inst. Sci. Res. Cancer, Villejuif, France), H. G. Suarez, S. Estrade and R. Cassingena. *Int J Cancer* 13(3):311-318, 1974.

Nonshedding simian virus 40 (SV40)-transformed cells reproducibly yield small amounts of infectious viral DNA after treatment with extracts of permissive cells in the presence of poly(L-ornithine), a basic polymer which increases the cellular uptake of protein. The factor(s) responsible for

rescue of the SV40 genome from the transformed cells (TS V-5 C12 hamster cells) (activator) is essentially detected in nuclear extracts from permissive cells (BSC-1 African green monkey kidney cells). Removal of the nucleic acids from these extracts with streptomycin improves their activating capacity on transformed cells. By increasing the yield of infectious virus DNA, the virions become frequently detectable. For a given experiment, a correlation is obtained between the protein concentration of the extract and the yield of infectious SV40 DNA. Unlike nuclear extracts from normal or SV40-transformed permissive cells, those from normal nonpermissive (EHB and BHK₂₁ C113) cells are ineffective in rescuing the viral genome. The biological activity of the factor(s) is preserved at 70 C for at least 3 months.

- 1396 VIRUS PARTICLES IN PRIMORDIAL GERM CELLS OF FETAL GUINEA PIGS. (E.) Black, V. H. (New York U. Med. Ctr., N.Y.). *J Natl Cancer Inst* 52(2):545-551, 1974.

Virus particles morphologically similar to those observed in cells from leukemic and normal guinea pigs were found in the primordial germ cells of fetuses from nonleukemic, random-bred guinea pigs. The spherical particles were 85-110 mμ in diameter and had two electron-dense shells surrounding a less dense core. They acquired their outer shell by budding into cisternae of the endoplasmic reticulum, and had a definite layer separating this membranous envelope from the inner shell. Filamentous projections were associated with the outer envelope. From their morphology, the intracisternal particles seen in the endoplasmic reticulum of cells in guinea pig fetuses and adults are probably RNA viruses. Their presence in fetal primordial germ cells suggests the vertical transmission of oncogenic RNA viruses directly through the germ cell line.

- 1397 CHARACTERIZATION OF AN ENDOGENOUS RNA-DEPENDENT DNA POLYMERASE ASSOCIATED WITH MURINE INTRACISTERNAL A PARTICLES. (E.) Yang, S. S. (Natl. Cancer Inst., Bethesda, Md.) and N. A. Wivel. *J Virol* 13(3):712-720, 1974.

An RNA-dependent DNA polymerase associated with intracisternal A particles from N-18 neuroblastoma cells and a mouse plasma cell tumor (MOPC-104E) was characterized. The enzyme required Mg^{2+} or Mn^{2+} , dithiothreitol and the presence of all four deoxyribonucleoside triphosphates for the expression of maximal activity. Sensitivity of the endogenous RNA-dependent DNA polymerase activity to a low concentration of pancreatic ribonuclease in the presence of a high concentration of NaCl suggested that the enzyme might be utilizing the A particle endogenous RNA as template. Evidence in support of this was provided by analyses of early and late DNA products of the endogenous reaction by Cs₂SO₄ isopycnic gradient centrifugation and hybridization of purified 60 to 70S and 35S RNAs of A particles with the purified DNA product.

1398-1401)

398 NEOPLASTIC TRANSFORMATION *IN VIVO* AND *IN VITRO* OF REGENERATING HAMSTER HEPATIC CELLS BY ONCOGENIC DNA SIMIAN VIRUS 40. (E.) Diamandopoulos, G. T. (Harvard Med. Sch., Boston, Mass.). *J Natl Cancer Inst* 52(1):139-145, 1974.

Three-wk old male Syrian golden hamsters were partially hepatectomized. At various times after surgery, some of the animals were inoculated i.v. with the oncogenic DNA simian virus 40 (SV40). Other animals were killed; their regenerating livers were excised and grown in culture in the presence of SV40. In both the *in vivo* and *in vitro* systems, only hepatic stromal, sinusoidal, and ductal-epithelial cells transformed neoplastically. Hepatic parenchymal cells did not develop oncogenic properties and, as a result, did not induce hepatocellular adenomas or carcinomas. The results indicated that resistance of hepatic parenchymal cells to the oncogenic effect of SV40 persisted, even with stimulation of their proliferative capacity before virus exposure. The significance of these observations is emphasized in regard to the association of hepatic parenchymal cell hyperplasia with neoplasia in man. Although cellular hyperplasia may be necessary for neoplastic cell transformation, it is apparently not a sufficient precondition in itself. Other factors relating to the host or to the oncogenic agent may be necessary for the initial transformation and subsequent survival of the neoplastic cell.

1399 POLY(2'-O-METHYLCYTIDYLATE) OLIGODEOXYGUANYLATE AS A TEMPLATE FOR THE RIBONUCLEIC ACID DIRECTED DEOXYRIBONUCLEIC ACID POLYMERASE IN RIBONUCLEIC ACID TUMOR VIRUS PARTICLES AND A SPECIFIC PROBE FOR THE RIBONUCLEIC ACID DIRECTED ENZYME IN TRANSFORMED MURINE CELLS. (E.) Gerard, G. F. (St. Louis J. Sch. Med., Mo.), F. Rottmann and M. Green. *Biochemistry* 13(8):1632-1641, 1974.

The potential of the 2'-O-methylated polynucleotides, poly(2'-O-methyladenylate), poly(2'-O-methylinosinate), poly(2'-O-methyluridylate), and poly(2'-O-methylcytidylate) (poly(Cm)), as specific templates for viral RNA directed DNA polymerase was evaluated. Of the four homopolymers, poly(Cm) complexed to a complementary oligodeoxyribonucleotide was the most effective template for the purified RNA directed DNA polymerase from virions of the avian myeloblastosis virus. The optimal metal ion concentrations for poly(Cm)·oligo(dG)-directed DNA synthesis catalyzed by avian myeloblastosis virus DNA polymerase were 0.15 mM Mn²⁺ and 5-10 mM Mg²⁺. The rate of synthesis was 40-fold greater with Mn²⁺ than with Mg²⁺. Poly(Cm)·oligo(dG) was an effective template for the RNA directed DNA polymerase of RNA tumor viruses of avian, murine, feline, and primate origin. None of the 2'-O-methylated homopolymers served as templates for *Micrococcus luteus* DNA polymerase or *Escherichia coli* DNA polymerase I. At least four different DNA polymerases were purified by DEAE-cellulose and phosphocellulose chromatography, and Sephadex G-200 gel filtration from extracts of a clonal line of mouse 3T6 fibroblast cells transformed by the Harvey strain of murine sarcoma-leukemia virus. Among the four enzymes, only the DNA polymerase that was identified as a

viral RNA directed DNA polymerase was able to use poly(Cm)·oligo(dG) as template. Nontransformed mouse 3T6 cells contained no detectable DNA polymerase activity which responded to poly(Cm)·oligo(dG) as template.

1400 SMALL, VIRUS-LIKE PARTICLES DETECTED IN BOVINE SERA BY ELECTRON MICROSCOPY. (E.) Benz, E. W., Jr. (Mayo Clin. Fdn., Rochester, Minn.) and H. L. Moses. *J Natl Cancer Inst* 52(6):1931-1934, 1974.

Twenty-two samples of bovine sera were examined by ultracentrifugation and electron microscopy for the presence of virus-like structures. All samples, including those of "virus-screened" fetal bovine serum (FBS) and agamma calf serum, had such structures. When pellets of FBS were resuspended in buffer and spun to equilibrium on a continuous 1.1-1.3 g/cc CsCl gradient, virus-like particles identical to those seen in the FBS pellets were observed in fractions with a density of 1.16-1.18 g/cc. In samples of FBS used to support the growth of two human lymphoblastoid cell lines from patients with acute infectious mononucleosis, peak incorporation of radioactive uridine was observed in the 1.17-1.18 g/cc densities; fractions with the highest radioactivity also contained the most small, virus-like particles. Contamination of FBS by such virus-like particles is a potential obstacle to studies attempting to detect and propagate a human tumor virus.

1401 ACTIVATION OF A C-TYPE VIRUS FROM THE HUMAN CARCINOMA CELL LINE HBT-3 BY IODODEOXYURIDINE AND TESTOSTERONE. (E.) Holder Jun, W. D. (Natl. Cancer Inst., Bethesda, Md.), W. G. Robey and G. F. Vande Woude. *Nature* 249(5459):759-762, 1974.

Human breast tumor (HBT-3Ep) cells were grown in the presence or absence of 5 µg/ml testosterone acetate. After 8 wk of cultivation with testosterone, contact-inhibited spindle-shaped cells (HBT-3S) began to appear; within 4 days, these cells comprised 90% of the population and on subsequent passage no epithelial cells were evident. If the testosterone was removed within 2 wk after the morphological change of the HBT-3Ep cells to the HBT-3S form, the change was reversed within 2-3 wk; the change was not reversible if the testosterone was removed more than 2 wk after the appearance of the HBT-3S cells. Electron microscopic examination revealed no virus particles in either the HBT-3Ep or HBT-3S cells; nor was any significant level of RNA-dependent DNA polymerase activity detected in the cell-free supernatant of either cell type. Treatment with iododeoxyuridine (IUDR) produced detectable C-type virus in the HBT-3S cells but not the HBT-3Ep cells. Primary immunological evaluation of the virus revealed a lack of activity with antisera to rat, murine, feline, and primate viruses. Repeated attempts to cultivate this virus in human and other mammalian cells have been unsuccessful and the virus does not have an observable effect on HBT-3Ep or HBT-3S cells. I.p. and s.c. inoculations into BALB/c mice produced no patho-

logical changes within 4 months. The data suggest that testosterone, together with TUDR has a derepressing action on the viral genetic information within HBT-3S cells.

- 1402 EFFECT OF MITOTIC INHIBITORS ON C-TYPE VIRIONS PRODUCTION. (E.) Hino, S. (Inst. Med. Sci., U. Tokyo, Japan) and T. Yamamoto. *Japan J Exp Med* 44(1):55-62, 1974.

The effect of mitotic inhibitors on the replication of C-type virus was studied to determine the possible relationship between the growth of these particles and the microtubular protein. By treating Friend leukemia virus-producing C3H2K cells with Colcemid or Vinblastin, the amount of tritiated uridine incorporated into the virions was reduced by 1/2 to 3/4; the incorporation of tritiated uridine into the cells and macromolecular cellular fraction was not inhibited. The inhibition of the incorporation into the virions was reversed by the removal of the mitotic inhibitors, indicating that the inhibition was not due to nonspecific cellular damage. The inhibition appeared within 1 hr and the rate of inhibition was not related to the increase of the cell population in mitotic arrest. This indicates that the inhibition was due to a different mechanism than that involved in the mitotic arrest of the cells. Direct binding of colchicine, a derivative of Colcemid, to the virions or viral subunits was not observed. These data did not support any relationship between viral assembly and cellular microtubular protein.

- 1403 PRIMATE AND MURINE TYPE-C VIRAL NUCLEIC ACID ASSOCIATION KINETICS: ANALYSIS OF MODEL SYSTEMS AND NATURAL TISSUES. (E.) Scolnick, E. M. (Nat'l. Cancer Inst., Bethesda, Md.), W. Parks, T. Kawakami, D. Kohne, H. Okabe, R. Gilden and M. Hatanaka. *J Virol* 13(2):363-369, 1974.

The single-stranded ^3H -DNA transcript of the type-C viruses isolated from the woolly monkey and gibbon ape were used in hybridization studies to investigate the distribution of these viruses in primates. The results were compared with those obtained in studies in which type-B and type-C viruses in mice were employed as model systems. The ^3H -DNA transcript from RIII mouse mammary tumor virus (M-MTV) (type-B virus) and the Kirsten strain of murine type-C virus (Ki-MuLV) RNAs hybridized readily to all mouse tissue DNAs examined, including L8A clone 11 DNA, BALB/c 3T3 DNA, NIH 3T3 DNA, and DNA derived from a fetal mouse cell culture line. Nonmurine DNAs from rat, human, and calf thymus gave no detectable hybridization with the murine type-B and C ^3H -DNA transcripts. Sheared DNA from human cells infected with woolly monkey type-C virus or gibbon type-C virus readily hybridized to the woolly monkey viral ^3H -DNA probe, while clinically normal woolly monkey, gibbon, marmoset, rhesus, African green monkey, chimpanzee, and human acute lymphoblastic and myelocytic leukemic DNAs failed to hybridize to the radioactive probe. Rat cellular DNA and calf thymus DNA also failed to hybridize significantly with the transcript.

The woolly monkey sarcoma genome present in the HT-1 type of nonproducer rat cells contained nucleic acid sequences homologous to the woolly monkey helper virus, and the ^3H -DNA transcript used detected the sequence in the DNA of such cells. The gibbon type-C virus ^3H -DNA probe readily hybridized to DNA from cells infected with gibbon virus and the 60-70S RNA prepared from the gibbon virus, but failed to give appreciable hybridization to uninfected gibbon liver DNA, DNA from human placenta, fresh ALL and AML cells, cells from rat, rabbit, or guinea pig liver. It is possible that all primate cells do not contain complete copies of the C-type viruses, or, alternatively, that the viruses thus far isolated from the woolly monkey and gibbon ape may have originated in another species and seldom if ever undergo vertical transmission in primates.

- 1404 ENDOGENOUS RAT C-TYPE VIRUS IN TRANSPLANTABLE RAT TUMORS. (E.) Hino, S. (Inst. Med. Sci., U. Tokyo, Japan), K. Yoshida, J. Enomoto, S. Oboshi and T. Yamamoto. *Japan J Exp Med* 44(2):179-189, 1974.

A culture line was established from a chemically induced rat ascites hepatoma (AH109A) in which C-type particles had been observed electron microscopically. Virions purified from the culture fluid were characterized immunologically. Rabbit antisera against 109A virus and anti-murine gs antisera were compared with each other by double diffusion tests. The anti-109A virus antiserum did not show any precipitation line against antigen preparations obtained from normal mouse or rat embryo or spleen or against a variety of murine C-type viruses. The anti-109A virus antiserum detected two kinds of antigen: one was specific for 109A virus and the other was common to murine and 109A viruses. Cross reactivity between the anti-109A virus antiserum and the anti-murine gs antiserum was not observed during immunoelectrophoresis. Some 20 lines of transplantable rat tumors, passages in culture and/or *in vivo*, were comparatively studied for antigenicity against the anti-109A antisera. Eighty percent of the lines passaged in culture and 35% of the lines passaged *in vivo* were highly antigenic.

- 1405 PLASMINOGEN, THE SERUM PROENZYME ACTIVATED BY FACTORS FROM CELLS TRANSFORMED BY ONCOGENIC VIRUSES. (E.) Quigley, J. P. (Rockefeller U., New York, N.Y.), L. Ossowski and E. Reich. *J Biol Chem* 249(13):4306-4311, 1974.

The serum factor which participates in the fibrinolytic activity associated with tumor and transformed cells was purified from dog, chicken, human, and fetal bovine sera. More than 90% of the serum factor given rise to fibrinolysis on interaction with cell factor was recovered in the fraction precipitating between 20 and 40% of saturation with ammonium sulfate. The chromatographic, electrophoretic, and biochemical properties of this molecule were consistent with the properties of the known fibrinolytic precursor, plasminogen. Purified plasminogen was isolated by affinity chromatography from crude fetal bo-

vine, chicken, dog, and human sera. Four purified plasminogens were tested for activation by cell factors from several transformed cultures and human tumor cell lines. The specificity of activation was absolute in the avian system in that chick plasminogen was activated only by the factor from cultures of chick embryo fibroblasts transformed by the Rous sarcoma virus. The mammalian plasminogens were activated to varying extents by the activators from all transformed cells tested.

- 1406 INCORPORATION OF VIRAL GENOME IN DNA OF CHRONICALLY INFECTED CELLS. (E.) Zhdanov, V. M. (D. I. Ivanovsky Inst. Virol., Moscow, USSR), O. G. Andzhaparidze and N. N. Bogomolova. *Experientia* 30(5):499-501, 1974.

³H-labeled viral RNA from the tick-borne encephalitis virus (TBEV) was mixed with an excess of DNA from HEp2 cells, some of which were chronically infected with TBEV. The RNA-DNA mixture was incubated at 37 C for 16 hours and centrifuged in cesium sulfate density gradients. The TBEV RNA banded at 1.65 g/ml in the cesium sulfate gradients. Hybridization of the viral RNA with DNA from the noninfected HEp2 cells did not significantly change the distribution of the radioactive label in the gradient, while hybridization of the viral RNA with DNA from chronically infected cells did significantly change the distribution of the label. A portion of the label in the latter case banded at the 1.45 g/ml which is characteristic for DNA labeled with fragments of RNA, and another portion occupied the density zone 1.60-1.52 g/ml which is characteristic of RNA:DNA hybrids. Thus, the genome of HEp2 cells chronically infected with TBEV contains DNA sequences which are homologous to the viral RNA; such sequences are absent from the genome of noninfected HEp2 cells.

- 1407 THE SYNTHESIS OF VIRAL ANTIGENS IN CYTOMEGALOVIRUS-INFECTED CELLS. (E.) DeMarchi, J. M. (State U. New York, Buffalo). *Diss Abs Int* 35(3):1328-B-1329-B, 1974.

- 1408 ENDOGENOUS GUINEA PIG ONCORNAVIRUS: ANALYSIS OF THE INDUCTION AND CHARACTERIZATION OF THE VIRUS PARTICLES. (E.) Murray, P. R. (U. California, Los Angeles). *Diss Abs Int* 35(3):1334-B, 1974.

- 1409 GLYCOSAMINOGLYCAN SYNTHESIS IN CULTURED SIMIAN VIRUS 40 TRANSFORMED HUMAN SKIN FIBROBLASTS. (E.) Hopwood, J. J. (U. Chicago, Ill.). *Fed Proc (II)* 33(5):1557, 1974.

- 1410 BURKITT'S LYMPHOMA AND OESOPHAGEAL CARCINOMA: ELECTRON MICROSCOPIC STUDIES OF BIOPSY AND TISSUE CULTURE FROM CASES OF. A REPORT FOR THE NATIONAL CANCER ASSOCIATION OF SOUTH AFRICA VIRUS-CANCER UNIT. (E.) Spence, I. M. (No affiliation). *S Afr Cancer Bull* 17(4):148-149, 1973.

- 1411 EFFECTS OF INHIBITORS OF PROTEIN AND NUCLEIC ACID SYNTHESIS ON THE EXPRESSION OF H-2 AND MOLONEY LEUKEMIA VIRUS-DETERMINED CELL-SURFACE ANTIGENS ON CULTURED MURINE LYMPHOMA CELLS. (E.) Cikes, M. (Karolinska Inst., Stockholm, Sweden) and G. Klein. *J Natl Cancer Inst* 48(2):509-522, 1972.

- 1412 STUDY ON C¹⁴-ACRYLAMIDE RADICAL CO-POLYMERIZATION AND H³-THYMIDINE INCORPORATION IN THE RAT FIBROBLAST CULTURE UNDER ADENOVIRAL INFECTION. (Rus.) Agenko, A. I. (P. A. Herzen Res. Inst. Oncol., Moscow, USSR), P. V. Gulak, I. Ya. Kogan, Ju. P. Kozlov. *Vopr Onkol* 20(9):80-82, 1974.

- 1413 STUDIES OF ERYTHROPOIESIS IN ERYTHROLEUKEMIC CELL CULTURES. (Ger.) Ostertag, W. (Max Planck Inst. Exp. Med., Gottingen, Germany), N. Kluge, H. Melderis, G. Steinheider, G. Gaedicke and S. Dube. *Verhandl Dtsch Ges Inn Med* 79:434-436, 1973.

- 1414 ENHANCED DEVELOPMENT OF RETICULUM CELL NEOPLASMS FOLLOWING SUBCUTANEOUS INOCULATIONS OF CELL-FREE FILTRATE OF EHRLICH'S ASCITES CARCINOMA. A STUDY IN ADULT, FEMALE MICE. (E.) Myking, A. O. (Dept. Pathol., U. Bergen, Norway). *Acta Pathol Microbiol Scand (A)* 84(2):564-570, 1974.

- 1415 A HEAT LABILE FACTOR RELATED TO THE DEVELOPMENT OF RETICULUM CELL NEOPLASMS TYPE B FOLLOWING INTRAPERITONEAL INOCULATIONS OF CELL-FREE FILTRATE OF EHRLICH'S ASCITES CARCINOMA. A STUDY OF ADULT, MALE MICE. (E.) Myking, A. O. (Dept. Pathol., U. Bergen, Norway). *Acta Pathol Microbiol Scand (A)* 82(4):578-581, 1974.

- 1416 STUDIES ON A UNIQUE ASPARTYL-TRANSFER RIBONUCLEIC ACID APPEARING IN SV40-INDUCED AND OTHER TUMORS. (E.) Briscoe, W. T. (U. Texas Hlth. Sci. Ctr., Houston). *Diss Abs Int* 35(3):1309-B-1310-B, 1974.

- 1417 MACROMOLECULAR SYNTHESIS IN CELLS INFECTED BY FROG VIRUS 3 II. EVIDENCE FOR POST-TRANSCRIPTIONAL CONTROL OF A VIRAL STRUCTURAL PROTEIN. (E.) Goorha, R. (St. Jude Children's Res. Hosp., Memphis, Tenn.) and A. Granoff. *Virology* 60(1):251-259, 1974.

- 1418 BIOCHEMICAL STUDIES OF MALIGNANT TRANSFORMATION AT THE CELLULAR LEVEL. 3. BIOCHEMICAL ASPECTS OF MALIGNANT TRANSFORMATION. (E.) Harington, J. S. (Natl. Cancer Assoc. South Africa, Johannesburg) and Gilbert. *S Afr Cancer Bull* 17(4):168-170, 1974.

- 1419 INHIBITION OF AMV DNA POLYMERASE BY POLY-RIBOADENYLIC ACID CONTAINING ϵ -ADENOSINE RESIDUES. (E.) Chirikjian, J. G. (Sch. Med. Dent., Georgetown U., Washington, D. C.) and T. S. Papas. *Biochem Biophys Res Commun* 59(2):489-495, 1974.

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- 1423 EFFECTS OF SUCCINYL-CON A ON THE GROWTH OF NORMAL AND TRANSFORMED CELLS. (E.) Trowbridge, I. S. (Salk Inst., San Diego, Calif.) and D. A. Hilborn. *Nature* 250(5464):304-309, 1974.
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- 1426 MACROMOLECULAR SYNTHESIS IN CELLS INFECTED BY FROG VIRUS 3. I. VIRUS-SPECIFIC PROTEIN SYNTHESIS AND ITS REGULATION. (E.) Goorha, R. (St. Jude Children's Res. Hosp., Memphis, Tenn.) and A. Granoff. *Virology* 60(1):237-250, 1974.
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- 1431 CO-ELECTROPHORESIS OF dsRNA FROM WOUND TUMOUR AND RICE DWARF VIRUSES. (E.) Reddy, D. V. R. (Provisional Dept. Genetics, Development, U. Illinois, Urbana), I. Kimura and L. M. Black. *Virology* 60(1):293-296, 1974.
- 1432 THE EFFECT OF FOLIC ACID AND OF METHOTREXATE ON REPRODUCTION OF THE VIRUS OF RAUSCHER'S LEUKEMIA. (Rus.) Shobukhov, V. M. (USSR Acad. Med. Sci., Moscow) and G. A. Galegov. *Biull Eksp Biol Med* 78(7):85-86, 1974.
- 1433 KERATOACANTHOMA IN A SMALLPOX VACCINATION SITE. (E.) Haider, S. (Roy. Free Hosp., London, England). *Br J Dermatol* 90(6):689-690, 1974.
- 1434 COMPLICATIONS OF SMALLPOX VACCINATION: BASAL CELL CARCINOMA, KELOIDS, ACUTE BULLOUS REACTION. (E.) Gordon, H. H. (Kaiser Fdn. Hosp., Fontana, Calif.). *Cutis* 13(3):444-447, 1974.
- 1435 CONTINUOUS CELL CULTURE FROM LYMPHOMA OF MAREK'S DISEASE. (E.) Akiyama, Y. (Res. Inst. Microbial Dis., Osaka U., Japan), S. Kato and N. Iwa. *Biken J* 16(4):177-179, 1973.
- 1436 INTRACRANIAL TUMOURS INDUCED IN GUINEA PIGS WITH ROUS SARCOMA VIRUS. (E.) Ahlstrom, C. G. (Dept. Pathol., U. Lund, Sweden), T. Olin and B. Smittberg. *Acta Pathol Microbiol Scand (A)* 82(2):326-336, 1974.
- 1437 ULTRASTRUCTURAL STUDY OF HETEROKARYONS FROM ROUS RAT SARCOMA CELLS AND NORMAL CHICKEN CELLS. (E.) Lindberg, L. G. (Inst. Pathol., U. Lund, Sweden). *Acta Pathol Microbiol Scand (A)* 82(2):299-310, 1974.
- 1438 HISTOPATHOLOGIC AND CYTOPHOTOMETRIC STUDY OF DYSPLASTIC AND PRECANCEROUS CONDYLOMA ACUMINATA. (Ger.) Jagella, H. P. (U. Clin., Hamburg-Eppendorf, Germany) and H. E. Stegner. *Arch Gynaekol* 216(2):119-132, 1974.

See also:

- * (Rev): 1208, 1218, 1220, 1225
- * (Chem): 1266, 1281
- * (Immun): 1446, 1463, 1467, 1468, 1472, 1473, 1480, 1483, 1484, 1490, 1494, 1501, 1503, 1507, 1523
- * (Epid-Biom): 1569, 1572, 1581, 1582, 1590

- 1439 SERUM INHIBITORY FACTORS IN CANCER. (E.) Suciú-Foca, N. (Coll. Physicians, Surg., Columbia U., New York, N.Y.), J. A. Buda, P. L. Gerfo, A. Moulton, C. Weber, B. Wheeler and K. Reemtsma. *Oncology* 29(3):219-226, 1974.

The cellular response and serum blocking factors of 70 cancer patients were assessed by micro-mixed lymphocyte culture and phytohemagglutinin techniques. Serum level of carcinoembryonic antigen (CEA) was determined by radioimmunoassay, and an attempt was made to correlate the concentration of CEA with the inhibitory effect of each serum on the blastogenic response of lymphocytes from cancer and healthy subjects. A direct correlation was found between the serum inhibitory activity, the CEA level, and the extent of the disease. CEA negative cancer sera, however, also inhibited transformation of autologous and normal homologous lymphocytes. This indicates that circulating CEA does not account for serum blocking activity.

- 1440 FUNCTIONAL STUDIES OF T AND B LYMPHOCYTES IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA. (E.) Thong, Y. H. (Georgetown U. Sch. Med., Washington, D.C.), R. A. Binder, L. Z. Sverak and J. A. Bellanti. *South Med J* 67(2):138-141, 1974.

The lymphocyte responsiveness of ten patients with chronic lymphocytic leukemia was studied with respect to B and T cell function. A depression in responsiveness to phytohemagglutinin and pokeweed mitogen and in mixed lymphocyte cultures was observed. The percentage of T cells in the circulating lymphoid pool was also decreased as measured by the rosette-formation test. These results suggest that the depressed T cell function may be related to a dilutional effect owing to the large number of B cells known to occur in this disease.

- 1441 HUMAN MYELOMA MARROW CELLS IN IMMUNOLOGICALLY DEFICIENT MICE. (E.) Mitchell, D. N. (Brompton Hosp., London, England), R. J. W. Rees and A. J. Salisbury. *Br J Cancer* 30(1):33-41, 1974.

Intact human bone marrow cells from seven patients with myelomatosis were inoculated i.v. into adolescent CBA mice rendered immunologically deficient by thymectomy followed by total body irradiation (600 rad). Each inoculum of human myeloma marrow cells and subsequent passages of intact mouse marrow and spleen cells resulted in morphological changes in the marrow, spleen, and peripheral blood of a proportion of these mice; these changes were closely similar to those seen in the human donor. A substantial amount of human immunoglobulin (IgG and IgA) was detected in the sera of some of the mice showing morphological changes. Mice prepared identically but remaining uninoculated or receiving intact human bone marrow cells from three patients with no evidence of hematological malignancy showed none of these changes when examined after similar intervals. In mice receiving human myeloma marrow

cells, the findings might be accounted for by the persistence and replication of these cells in an immunologically deficient host. In mice receiving a first, second, or third passage of abnormal mouse marrow and spleen cells, the findings might be explained in terms of the survival and multiplication of a stem cell secreting both mouse and human immunoglobulins. Alternatively, the mouse stem cells may in some way have been transformed following infection by a transmissible agent originally present in the myeloma donor marrow cells.

- 1442 MONOCLONAL LYMPHOCYTE POPULATION IN HUMAN PLASMA CELL MYELOMA. (E.) Mellstedt, H. (Dept. Med., Serafimer Hosp., Stockholm, Sweden), S. Hammarström and G. Holm. *Clin Exp Immunol* 17(3):371-384, 1974.

To identify monoclonal bone marrow-derived (B) lymphocytes in human myelomatosis, specific rabbit antisera were produced against idiotypic specificities on IgG-K myeloma proteins from three patients. The antisera neither cross-reacted nor reacted with normal immunoglobulins. By indirect immunofluorescence, surface immunoglobulins were observed on 20-47% of the peripheral blood lymphocytes of untreated patients after staining with idiotypic antiserum against the patient's own myeloma protein; these surface immunoglobulins were not seen after staining with other idiotypic antisera. The antisera also stained autologous plasma cells. The monoclonal surface Ig on the myeloma lymphocytes was removed by trypsin and regenerated after incubation in serum-free medium. Myeloma protein was not absorbed onto lymphocytes. These data indicate that monoclonal B lymphocytes belonging to the plasma cell myeloma clone are present in myeloma patients. There were few normal B lymphocytes in untreated patients. During treatment, however, the monoclonal lymphocyte population and the plasma cell content in the bone marrow, as well as the concentration of monoclonal immunoglobulin, decreased simultaneously. These findings were associated with other signs of clinical improvement.

- 1443 CARCINOEMBRYONIC ANTIGEN IN CANCER OF THE FEMALE REPRODUCTIVE SYSTEM: ITS DETECTION IN SERUM BY A MICRORADIOIMMUNOASSAY. (E.) Khoo, S. K. (Clin. Res. Unit, Walter Eliza Hall Inst. Med. Res., Roy. Melbourne Hosp., Australia) and E. V. Mackay. *Aust NZ J Obstet Gynaecol* 13(2):107-113, 1974.

A microradioimmunoassay technique was used to detect carcinoembryonic antigen (CEA) in the sera of 167 patients with various cancers of the female genital organs, 30 patients with breast cancer, 138 patients with cancer of the digestive system, 73 patients with benign gynecological conditions, and 130 controls. CEA in excess of 5 ng/ml was found in 95% of the patients with cancers of the digestive system, 60% of the patients with cancers of the female reproductive system, none of the patients

with benign gynecological conditions, and 4% of the controls. Among the first group of patients, the highest incidences of positive results were obtained in the patients with ovarian (73%) and breast (70%) cancer. The incidence of high levels of CEA (values of 10 ng/ml or greater) was lower in the patients with reproductive system cancers (56) than in those with cancers of the digestive system (96). There was no difference in the incidence of positive results among patients with adenocarcinoma and squamous cell carcinoma of the female genital organs. In general, a higher incidence of positive results and higher levels of CEA were found in patients with extensive or metastatic disease, but positive results were found even in those with pre-invasive lesions (carcinoma *in situ* and severe dysplasia).

1444 IMMUNOGENETIC ASPECTS OF NASOPHARYNGEAL CARCINOMA. II. ANALYSIS OF ABO, RHESUS AND MNSS RED CELL SYSTEMS. (E.) Hawkins, B. R. (Dept. Path., IARC Res. Ctr., Singapore), M. J. Simons, E. H. Goh, D. B. Chia and K. Shanmugaratnam. *Int J Cancer* 13(1):116-121, 1974.

The distribution of red cell antigens of the ABO, Rhesus, MNSS, and P systems was studied in 102 Chinese nasopharyngeal carcinoma (NPC) patients from Singapore, Malaysia, and Hong Kong, in 166 Singapore blood donors, and in 43 Singapore Chinese who were suspected of having NPC but in whom malignancy was not detected histologically. No statistically significant differences were found in either the phenotype or genotype frequencies between the three groups. The results of surveys investigating the possible association between blood groups and NPC are reviewed. If the hypothesis of a genetic predisposition to NPC is correct, it appears unlikely that the blood group genes which were studied are involved, at least as independently functioning genes. However, in Chinese patients, a systematic study of dialect subgroups is necessary before a conclusion can be drawn.

1445 RELATION OF CELL-MEDIATED IMMUNITY IN WOMEN WITH GENITAL TRACT CANCER TO ORIGIN, HISTOLOGY, CLINICAL STAGE AND SUBSEQUENT BEHAVIOUR OF NEOPLASM. (E.) Khoo, S. K. (U. Queensland, Dept. Obstet. Gynaecol., Roy. Brisbane Hosp., Australia) and E. V. Mackay. *J Obstet Gynaecol Br Commonwealth* 81(3):229-235, 1974.

A quantitative study of cell-mediated immunological reactivity was conducted using 99 patients with carcinoma of the uterine cervix, 40 patients with carcinoma of the corpus uteri, and 39 patients with ovarian carcinoma. Primary reactivity was measured in terms of sensitization to dinitrochlorobenzene (DNCB) and secondary reactivity was assessed in terms of delayed cutaneous hypersensitivity to skin test antigens (STA). In general, there was an increased incidence of anergic and impaired reactivity in the cancer patients compared with age-matched

controls. Differences between patient groups regarding organ of origin or histological type were small and nonsignificant. There was a progressive increase in the incidence of anergic and impaired reactivity with worsening of the clinical stage of the tumor. Significant differences in reactivity existed between patients who had remained free of disease after treatment and those who had progressive disease after 12 months of follow-up; the incidence of anergy was significantly increased in the latter group, although the incidence of impaired reactivity was comparable in the two groups. The impairment of cell-mediated immunity appears to be an unfavorable factor in host tumor interactions, and the possibility of augmenting immunological reactivity should be considered in the management of cancer cases.

1446 COMPARISON OF SV40 INDUCED ANTIGENS ON THE SURFACE OF CULTIVATED CELLS BY A CYTOLYTIC MICROASSAY. (E.) Pancake, S. J. (Nat'l. Cancer Inst., Bethesda, Md.) and P. T. Mora. *Virology* 59(1):323-327, 1974.

A direct cytolytic microassay technique was used to detect SV40 virus induced antigens on the surfaces of SV40 transformed intact cells of various origins. The SV40 specific antisera killed SV40 T antigen positive AL/N mouse cell lines, including lines which had been repeatedly passed through the syngeneic mouse as tumors. The sera also killed a polyoma transformed SV40 T antigen negative AL/N cell line, but did not affect untransformed or spontaneously transformed AL/N embryo cell lines. There was no lysis observed on SV40 T antigen positive Balb/c mouse, hamster, or human cell lines, although a competition assay showed SV40 specific common antigens on the surfaces of these cells. Thus, the direct cytolytic test is more stringent than the competition test. The results suggest that the common antigens of SV40 and polyoma transformed cells detected in these tests are not related to late embryonic features.

1447 ALTERED METABOLISM OF CARCINOEMBRYONIC ANTIGEN IN HAMSTERS BEARING GW-39 TUMOURS. (E.) Primus, F. J. (Dept. Immunol., Hoffmann-La Roche Inc., Nutley, N.J.), H. J. Hansen and D. M. Goldenberg. *Nature* 249(5460):837-838, 1974.

Female Syrian hamsters were heterografted with a carcinoembryonic antigen (CEA)-producing colonic adenocarcinoma of human origin and injected intracardially with 7-9 μ Ci of aggregate-free 125 I-CEA, which had been purified from liver metastases of human colonic adenocarcinomas. Compared with normal hamsters, the clearance of plasma radioactivity was decreased in animals bearing cheek pouch and i.m. GW-39 tumors, the decrease being more marked with the i.m. tumors. Within 60 min, the radioactivity in both the plasma and liver of the tumor-bearing hamsters was similar to that of normal animals, as was the distribution of radioactivity

among the other organs. The radioactivity which was present in 30 min and 3 hr liver samples from normal and tumor-bearing hamsters was characterized on Sepharose 6B columns. The first radioactivity peak in the 30 min sample from the normal animals chromatographed with the preinjection antigen, whereas in the 3 hr sample, this peak eluted at a slightly lower molecular weight. The second peak in both samples represented low molecular weight materials which lacked immunoreactivity with goat anti-CEA antibody; it formed 10-15% of the material in the liver. The radioactivity in the plasma of normal animals at 5 min was identical to the preinjection CEA. Subsequently, a low molecular weight, nonimmunoreactive radioactive peak, similar to that in the liver, gradually appeared and accompanied a decrease in the quantity of radioactive material which eluted as the preinjection CEA. In the 15 and 60 min plasma samples from the tumor-bearing animals, the major portion of the radioactivity represented the low molecular weight, nonimmuno-reactive material. The plasma radioactive macromolecule which appears in these animals is probably a CEA-antibody complex.

- 1448 PREPARATION AND ISOLATION OF IMMUNOLOGICALLY ACTIVE GLYCOPEPTIDES FROM CARCINOEMBRYONIC ANTIGEN (CEA). (E.) Banjo, C. (U. Med. Clin., Montreal Gen. Hosp., Quebec, Canada), P. Gold, C. W. Gehrke, S. O. Freedman and J. Krupey. *Int J Cancer* 13(2):151-163, 1974.

To determine the structure of the tumor-specific immunodominant group of the carcinoembryonic antigen (CEA) of human gastrointestinal tumors, immunologically active fragments from this glycoprotein were prepared by partial enzymatic hydrolysis using the proteolytic enzyme nagase. The fragments were purified by sequential molecular sieve, adsorption, and ion exchange chromatography, and were analyzed for carbohydrate and amino acid composition by gas-liquid chromatography. The antigenic activity of each fragment was tested using the Z-gel and Farr radioimmunoassay techniques for CEA. Nagase digestion produced a number of glycopeptide fragments which retained the tumor-specific grouping of the molecule and had molecular weights between 1000 and 5000 Daltons. All of the active fragments were largely carbohydrate in composition. To permit the action of nagase on the CEA molecule, it was necessary to remove the sialic acid residues in the CEA by neuraminidase treatment; all of the sialic acid residues were present in terminal positions of the carbohydrate portions of the CEA molecular, and sialic acid residues which are present in terminal nonreducing positions of the carbohydrate moiety of CEA do not play a role in the tumor-specific antigenic grouping of the molecule. All of the glycopeptide fragments had relatively high contents of N-acetyl-D-glucosamine, aspartic acid or asparagine, glutamic acid or glutamine, threonine, and proline. Galactose residues do not appear to play a significant role in the tumor-specific grouping of the CEA molecule, while N-acetyl-D-glucosamine probably plays a central role in the tumor-specific determinant group of the molecule. All six glycopeptides were immunologically active.

- 1449 CARCINOEMBRYONIC ANTIGEN-LIKE SUBSTANCES OF HUMAN UROTHELIAL CARCINOMAS: ISOLATION OF COMPONENTS FROM PATHOLOGICAL URINE AND COMPARISON WITH COLORECTAL CARCINOMA ANTIGENS. (E.) Nery, R. (Chester Beatty Res. Inst., London, England), A. L. Barsoum, H. Bullman and A. M. Neville. *Biochem J* 139(2):431-440, 1974.

Urine samples from several patients with urothelial carcinoma were studied by radioimmunoassay, various staining techniques, gel-filtration chromatography, electrophoresis on cellogel, disc electrophoresis on polyacrylamide gels, immunodiffusion in agarose, and CsCl density-gradient centrifugation. The samples contained inhibitors of the immunoreaction between carcinoembryonic antigen (CEA) derived from human colorectal carcinomas and monospecific goat antiserum raised against the antigen. These inhibitors ranged in approximate molecular weight from less than 1000 to several million. Two such inhibitors were isolated by a combination of extraction, gel filtration, and electrophoretic procedures: component UCEA-3, a macromolecular aggregate which was excluded by Sepharose 4B; and component UCEA-1, a glycoprotein(s) with a mean molecular weight (2×10^5) similar to that of CEA. Comparison of the properties of UCEA-1 and CEA via gel filtration, electrophoresis, immunoelectrophoresis, and density gradient ultracentrifugation indicated that these substances differed in terms of some immunochemical properties.

- 1450 CELL SURFACE ANTIGENS OF A MOUSE TESTICULAR TERATOMA. IDENTIFICATION OF AN ANTIGEN PHYSICALLY ASSOCIATED WITH H-2 ANTIGENS ON TUMOR CELLS. (E.) Gooding, L. R. (Dept. Biol., Johns Hopkins U., Baltimore, Md.) and M. Eddidin. *J Exp Med* 140(1):61-78, 1974.

Rabbit antisera to a mouse testicular teratoma, absorbed with normal mouse tissues, react by immunofluorescence with plasma membrane antigens of a variety of transplantable mouse tumor cells and transformed fibroblast cell lines, including Clone 1D, SV40-3T3, and 3T12. Trypsin treatment of the cells of "normal" lines, 3T3 and FR-SV-3T3, uncovers reactivity on these as well. Early passage mouse embryo fibroblast cell cultures do not react even after trypsinization. The results of cross-absorption studies indicate that the anti-teratoma serum appears to react with an antigen common to most tumor cells investigated thus far. When this antigen on Clone 1D cells is "capped," H-2 antigens collect with the teratoma antigens in the cap, indicating a physical association between the molecules. Molecules specified by both the H-2D and H-2K regions are bound to the teratoma antigens in the Clone 1D plasma membrane. This antigen is also found in soluble tumor cell fractions where it is believed to be free of H-2. A second cell surface antigen defined by anti-teratoma serum is expressed only by hepatoma and teratoma itself. This second antigen is apparently a secretory product of teratoma cells. A third surface antigen defined by anti-teratoma serum appears to be specific for the teratoma.

- 1451 IMMUNOCHEMICAL ANALYSIS OF THE IDIOTYPES OF MOUSE MYELOMA PROTEINS WITH SPECIFICITY FOR LEVAN OR DEXTRAN. (E.) Weigert, M. (Salk Inst., San Diego, Calif.), W. C. Raschke, D. Carson and M. Cohn. *J Exp Med* 139(1):137-147, 1974.

The relationship of idiootype to the combining activities of mouse myeloma proteins which bind dextran or levan was studied. As illustrated by the anti- $\alpha(1\rightarrow6)$ dextran mouse myeloma immunoglobulin W3129, the assay for ligand-modifiable determinants can be used to determine the "size" of the combining site. Whether the interaction between a homologous series of $\alpha(1\rightarrow6)$ oligosaccharide ligands and the combining site of W3129 is measured by inhibition of precipitation with $\alpha(1\rightarrow6)$ dextran or binding of W3129 to anti-W3129 idiootype, the finding is the same. The order of inhibition is isomaltotetraose = isomaltopentaose >> isomaltotetraose > isomaltotriose >>> isomaltose. The combining site is optimally complementary to isomaltopentaose. Cross-idiootype specificity is closely correlated with cross-combining specificity; the converse is not true. This was illustrated with three groups of mouse myeloma immunoglobulins, each specific for $\alpha(1\rightarrow3)$ dextran (J558, MOPC 104E, UPC 102, which cross-react with anti-J558), $\alpha(1\rightarrow6)$ -dextran (W3129 and W3434, which cross-react), or $\beta(2\rightarrow1)$ or $\beta(2\rightarrow6)$ levan (cross-reacting W3082, UPC 61, and Y5476). If a given anti-idiotypic serum cross-reacted with several myeloma proteins, they always had similar combining specificities. However, proteins may have specificity for dextran or levan, yet not carry the above-mentioned reference idiotypes. The correlation between cross-idiotypic and combining specificity breaks down when idiotypic determinants which are not modifiable by ligand are studied. Since amino acid substitutions which change the combining specificity of the antibody would not affect this class of idiotypic determinant, a given antiserum should recognize antibodies of unrelated specificity with reasonably high frequency if the shared idiotypic determinant is ligand nonmodifiable.

- 1452 STUDIES ON ANTIBODY SURVEILLANCE TO EBV VIRUS-INDUCED ANTIGEN IN PATIENTS WITH SARCOIDOSIS AND NASOPHARYNGEAL CARCINOMA BY INDIRECT IMMUNOFLUORESCENCE. (E.) Naiton, M. (Res. Inst. Microbial Dis., Osaka U., Japan), U. Akiyama, S. Kato, T. Tachibana and T. Sakai. *Biken J* 16(4):141-148, 1974.

The indirect immunofluorescence technique was used to examine Epstein-Barr virus (EBV) induced antibodies against viral antigen (VA) and early antigen (EA) in sera from 70 patients with sarcoidosis and 31 patients with nasopharyngeal carcinoma. Control sera were obtained from 120 patients with non-NPC neoplasms of the head and neck, 14 patients with tuberculosis, 40 other patients, 38 family members of NPC patients, and 94 healthy individuals. Dissociation in the frequency distribution of the anti-VA titers of the normal controls and patients with sarcoidosis or NPC were maximum when the limit for a positive reaction was set at 1:640. Of the sera from the sarcoidosis patients, 60.1% had anti-

VA titers equal to or greater than 1:640. There was no significant correlation between the anti-VA titers and the clinical stage of sarcoidosis, although sarcoidosis patients who had become clear of pulmonary x-ray findings, showed a somewhat lower positive rate of anti-VA activity, than patients with pulmonary x-ray findings of sarcoidosis. Among 108 controls, including those with tuberculosis and other diseases, 21.3% had VA antibody titers equal to or greater than 1:640. VA antibody titers of 1:640 or greater were found among 61.3% of the NPC patients, 28.3% of the non-NPC cancer patients, 7.9% of the relatives of the NPC patients, and 10% of the normal controls. The proportion of sera with anti-EA titers of 1:10 or greater was significantly higher in the NPC patients than in the sarcoidosis patients or healthy persons; the latter two groups did not differ in this respect. Thus, the mode of involvement of EBV in sarcoidosis differs from that in Burkitt's lymphoma and NPC.

- 1453 DELAYED-HYPERSENSITIVITY REACTIONS TO SOLUBLE MEMBRANE ANTIGENS OF HUMAN MALIGNANT LUNG CELLS. (E.) Hollinshead, A. C. (Dept. Med., George Washington U., Washington, D.C.), T. H. M. Stewart and R. B. Herberman. *J Natl Cancer Inst* 52(2):327-338, 1974.

Membrane preparations (0.1 ml amounts, containing 17-1232 μ g membrane protein) of human lung cancer cells, "normal" lung cells from the same patient, and normal lung cells from a healthy accident victim did not produce delayed hypersensitivity reactions in intradermal skin tests of lung cancer patients. In contrast, Sephadex G-200-separated soluble fractions, both high- and low-molecular wt, of the same preparations produced positive delayed reactions in autologous and allogeneic lung cancer patients. Lung cancer-sonicate fractions were reactive in 50 of 106 tests and "normal" lung-sonicate fractions from cancer patients were reactive in 19 of 106 tests. The high-molecular wt fraction of lung sonicate from the accident victim produced a borderline positive response in a patient with epidermoid lung cancer. Soluble antigens from epidermoid cancer cells gave positive tests in allogeneic testing of a patient with epidermoid lung cancer, whereas antigens from metastatic tumors in the lungs of intestinal and cervical cancer patients were nonreactive. The soluble antigens were further separated by special gradient gel electrophoresis and elution of sliced regions of the gels. Skin tests on nine patients with oat cell carcinoma, epidermoid carcinoma, and adenocarcinoma were performed with the soluble antigens from gel regions prepared from five tumors, five adjacent lung preparations, and healthy lung. The results show that regions I and II of the gels probably contain normal lung antigens, which can elicit a delayed-hypersensitivity response in some lung cancer patients. The antigens in regions II and IV appeared more tumor-associated. Nine patients with nonpulmonary tumors did not react with these regions of lung preparations.

- 1454 ALLOGENEIC BONE MARROW CHIMERISM IN GERM-FREE MICE. II. PREVENTION OF RETICULUM CELL SARCOMAS IN SJL/J MICE. (E.) Pollard, M. (Lobund Lab., U. Notre Dame, Ind.) and R. L. Truitt. *Proc Soc Exp Biol Med* 145(2):488-492, 1974.

Germ-free SJL/J mice were lethally irradiated and inoculated i.v. with viable bone marrow cells from germ-free C3H mice. Reticulum cell sarcomas did not develop in the chimeric germ-free SJL/J mice, while conventional counterpart mice died of graft-versus-host disease. Fourteen germ-free SJL/J mice, subjected only to the X-irradiation, died at an average of 8.7 days with symptoms of wasting, diarrhea, and pneumonia. At 11 months of age, 90% of 86 untreated conventional and 136 germ-free SJL/J mice developed gross evidence of a mixed-type reticulum cell sarcoma. Twenty irradiated conventional SJL/J mice, inoculated with bone marrow cells from adult conventional C3H mice, appeared healthy for several days, then showed clinical evidence of graft-versus-host disease and died at the average age of 21 days. Of the 11 germ-free chimeric SJL/J mice subjected to complete necropsy examination, all were symptom free between the ages of 10 and 15 months at termination of the study. No changes diagnostic of reticulum cell sarcoma were noted. Thus the development of reticulum cell sarcoma in germ-free SJL/J mice has been prevented by allogeneic chimerism.

- 1455 CANCER, AUTOIMMUNITY AND IgA-DEFICIENCY RELATED BY A COMMON ANTIGEN-ANTIBODY SYSTEM. (E.) Butler, J. E. (Dept. Microbiol., U. Iowa Coll. Med., Iowa City) and R. Oskvig. *Nature* 249(5460):830-833, 1974.

Routine indirect immunofluorescence screening of human biopsy material was undertaken to determine whether human or rabbit antibodies to bovine associated mucoprotein (BAMP) could react with human epithelial tissue. All normal human biopsies were negative, but striking cell membrane fluorescence was seen on all diagnosed human epithelial cell tumors, 12% of the renal transplant biopsies, many fetal epithelial cell membranes, and in systemic lupus erythematosus (SLE) skin biopsies. The positive human cells were always epithelial and showed the same characteristic 'rim' fluorescence seen in bovine tissues. When the sera of patients with precipitating antibodies to BAMP were tested on sections of human mammary carcinoma or normal bovine tissue in the indirect assay, positive fluorescence was obtained with both human and bovine tissues, particularly the former. The correlation between the presence of serum antibodies to BAMP and BAMP-positive biopsies in patients with SLE was (2/2), mammary carcinoma (3/3), melanoma (1/3), and positive kidney biopsies (1/5). No evidence was obtained for heterogeneity of antibodies to BAMP among patients with different disorders, nor was clear-cut evidence for a BAMP-related tumor antigen in the sera. The data suggest that BAMP is a bovine protein which is antigenically related to a carcinoembryonic antigen in man. Thus, BAMP can be called a phylo-carcinoembryonic antigen.

- 1456 TRANSFER OF CELL-MEDIATED SKIN REACTIVITY WITH "IMMUNE" RNA IN HODGKIN'S DISEASE AND OTHER NEOPLASTIC DISEASES. (E.) Han, T. (Roswell Pk. Mem. Inst., Buffalo, N.Y.). *Cancer* 33(2):497-502, 1974.

The adoptive transfer of delayed skin hypersensitivity to skin test antigens with "immune" RNA was studied in patients with Hodgkin's disease, lymphosarcoma, colonic carcinoma, bronchogenic carcinoma, reticulum cell sarcoma, cylindroma of the parotid gland, synovial cell sarcoma, neurofibrosarcoma, and metastatic adenocarcinoma. The "immune" RNA was obtained from the peripheral lymphocytes of a normal subject with strongly positive Varidase, monilia, and mumps skin test responses, from a patient with Hodgkin's disease in remission with positive intermediate strength purified protein derivative (PPD) skin test response after BCG vaccination, and from a Hodgkin's patient with positive Varidase and mumps skin test responses. The "immune" RNA obtained from the sensitized lymphoid cells of these donors was capable of transferring skin reactivity in a majority of the patients following intradermal injection a few centimeters from the site of the skin test or on the opposite forearm. The "immune" RNA was antigen-specific and systematically active, and there was good correlation between the outcome of the "immune" RNA-mediated transfer and the clinical features of the patients. The transfer was successful in a higher percentage of patients with localized disease, in remission, receiving no antitumor therapy, or with positive skin test response, compared to those with generalized disease, in active state of disease, receiving antitumor therapy, or with negative skin test response, respectively.

- 1457 LOCALISATION OF HUMAN α -FETOPROTEIN SYNTHESIS IN HEPATOBLASTOMA CELLS BY IMMUNO-FLUORESCENCE AND IMMUNOPEROXIDASE METHODS. (E.) Norgaard-Pedersen, B. (Dept. Clin. Chem., Natl. Hosp., Copenhagen, Denmark), E. Dabelsteen and C.-J. Edeling. *Acta Path Microbiol Scand* 82(2):169-174, 1974.

The indirect immunofluorescence (IF) and indirect immunoperoxidase (IP) techniques were used to demonstrate the presence of α -fetoprotein (AFP) in fetal liver tissue and in liver tissue samples from two cases of hepatoblastoma, one in a 2-yr-old boy and one in a 3-yr-old boy. In the first case, the AFP concentration in the serum was 308 mg/l prior to surgery (as determined by immunoelectrophoresis), 1 mg/l 4 wk after surgery, and 468 mg/l 6 months later; the patient died 1 yr after the initial admission with massive hepatoblastoma and widespread metastases. In the second case, the initial serum concentration was 206 mg/l and the concentration 10 days after surgery was 36 mg/l. The AFP concentrations in all of the fetal sera were above 1000 mg/l. In both the fetal and hepatoblastoma tissues, IF and IP demonstrated staining in the cytoplasm of the majority of hepatocytes.

- 1458 STUDIES ON LIVER CANCER. II. PRODUCTION OF α -FETOPROTEIN BY EXPERIMENTAL HEPATOMA AND ITS CHARACTERIZATION. (E.) Koda, T. (Res. Inst. Microbial Diseases, Osaka U., Japan), S. Ishigami and S. Tanabe. *Biken J* 16(4):129-139, 1974.

A monospecific rabbit antiserum against rat α -fetoprotein was used to determine the α -fetoprotein levels in pregnant and postpartum Donryu and Sprague-Dawley rats. In the pregnant animals, α -fetoprotein is found in the blood from the seventh day after conception. After delivery, it disappears rapidly and is not present in the blood 3 days later. α -Fetoprotein was present in the blood of the newborn rats until 4 wk after birth. In a second experiment, ascites hepatoma AH-130 cells were injected s.c. or i.p. into Donryu and Sprague-Dawley rats. α -Fetoprotein was detected in the serum of these animals from the fourth day after inoculation; the level gradually rose to a maximum shortly before the animals died. Immunodiffusion studies indicated that the α -fetoprotein in the serum and ascites of rats with 4-methylaminoazobenzene (DAB)-induced hepatomas was identical to that found in rats with transplanted AH-130 tumors. Cross-reactions between rat α -fetoprotein, human α -fetoprotein, and mouse α -fetoprotein were studied by immunodiffusion, immunoelectrophoresis, and immunofluorescence using a monospecific rabbit antiserum against rat α -fetoprotein; no positive results were obtained. While it was possible to transfer the AH-130 hepatoma to Sprague-Dawley rats, it could not be passed to xenogenic mice; similar findings were obtained with the mouse ascites hepatoma MH-134.

- 1459 *IN VIVO* LOCALISATION OF RADIOLABELLED ANTIBODIES TO CARCINOEMBRYONIC ANTIGEN IN HUMAN COLON CARCINOMA GRAFTED INTO NUDE MICE. (E.) Mach, J.-P. (Ludwig Inst. Cancer Res., Lausanne, Switzerland), S. Carrel, C. Merenda, B. Sordat and J.-C. Cerottini. *Nature* 248(5450):704-706, 1974.

Anti-CEA (carcinoembryonic antigen) antibodies were isolated by adsorption-elution from a specific immuno-adsorbent. The ^{125}I -labeled antibodies (2 μg) and normal goat 7S globulins (200 μg) were injected i.v. into nude mice bearing s.c. grafts of human colonic carcinomas. External scintillation scanning indicated that after 1 day, the radioactivity began to localize in the tumor areas, giving optimal detectable contrast by day 3. Dissection of the animals confirmed that the major radioactive site was related to the tumor and not to the adjacent liver. The antibody localization was then studied by simultaneous injection of ^{131}I -labeled antibodies and ^{125}I -labeled normal goat 7S globulins; in two experiments, the labels were reversed. The concentration of antibodies in the tumor was more than 2-fold greater than that of normal 7S, whereas in the normal tissues, the antibodies had lower values than the control protein. When the same experiments were performed in C57Bl/6 mice bearing transplanted EL4 solid lymphomas, the specificity indices were not significant. The specificity of antibody localization appeared to decrease in the presence of necrotic tissue within the tumor.

- 1460 RAT $\alpha_1\text{F}$. XI. IMMUNOLOGICAL CONTROL OF CELL PROLIFERATION: INCREASED GROWTH RATE AND $\alpha_1\text{F}$ PRODUCTION BY MORRIS HEPATOMA 5123tc IN RATS TREATED WITH ANTI-THYMOCYTE SERUM. (E.) Bernstein, P. (U. California San Diego Med. Sch., La Jolla), H. T. Wepsic and S. Sell. *Int J Cancer* 13(4):506-514, 1974.

Male Buffalo rats were inoculated i.m. with transplantable Morris hepatoma 5123tc cells and s.c. with antithymocyte serum (1 ml/100 gm). The animals had also been injected 6, 4, and 2 days previously with antithymocyte serum (ATS) and were given similar injections 2 and 4 days after tumor inoculation. The administration of ATS to the tumor bearing rats resulted in an increase in the growth rate of the tumor and in the rate of $\alpha_1\text{F}$ fetoprotein ($\alpha_1\text{F}$) production by the tumor. The amount of $\alpha_1\text{F}$ per gram of tumor tissue was also significantly greater in the ATS-treated animals. In addition, the mitotic index of the tumors in the ATS-treated rats was twice that of the tumors in the control animals. The results indicate that the rate of $\alpha_1\text{F}$ production by hepatomas which have the capacity to synthesize $\alpha_1\text{F}$ is directly related to the number of proliferating cells present at any given time. The data also indicate that the rate of growth of a tumor is not a fixed property of the tumor but may be accelerated by immunosuppression of the tumor-bearing animal.

- 1461 RELATIONSHIP OF ANTIGENICITY OF MELANOMA CELLS GROWN IN 5-BROMODEOXYURIDINE TO REDUCED TUMORIGENICITY. (E.) Silagi, S. (Cornell U. Med. Coll., New York, N.Y.), E. W. Newcomb and M. E. Weksler. *Cancer Res* 34(1):100-104, 1974.

B16 mouse melanoma cells (clone B559) grown in 1-3 μg 5-bromodeoxyuridine (BUdR)/ml formed few or no tumors in C57BL/6J adult mice when injected s.c. in doses at which untreated cells always form tumors. Injections of BUdR-grown cells protect adult mice against melanoma. Melanoma cells grown in 1 μg BUdR/ml for almost one yr (clone C3471) retained a plating efficiency similar to that of untreated cells. When C3471 cells were injected into C57BL/6J mice treated with antithymocyte serum or into neonates, tumors grew and killed all the mice. Melanoma cells grown in 3 μg BUdR/ml for 14 days formed no tumors in normal adult mice, but formed tumors and killed 72% of antithymocyte serum-treated adults and 21% of neonates inoculated with 10^6 cells. Although their plating efficiency is reduced from control levels, the ability of BUdR-treated melanoma cells to grow *in vivo* is proved by tumor formation in immunologically compromised mice. Growth in both concentrations of BUdR greatly increases production of a C-type virus. C3471 cells express Gross cell surface antigen, undetectable in control cells, and increase their expression of H-2^D antigen. The ability of BUdR-grown cells to protect against melanoma and to form tumors in neonates and antithymocyte serum-treated adults, in contrast to normal adults, and their increased production of virus and of cell surface antigens, indicate that one component of the loss of tumorigenicity is a change in antigenicity of these cells.

- 1462 DISTINCTION OF ALLOGENEIC IMMUNITY FROM TUMOR-SPECIFIC IMMUNITY IN MAN. (E.) Parks, L. C. (Johns Hopkins U. Sch. Med., Baltimore, Md.), W. J. Smith and G. M. Williams. *Surgery* 76(1):43-49, 1974.

Tissue-cultures melanoma cells and their autogenous fibroblasts were used in microcytotoxicity tests to determine the prevalence and activity of "killer" lymphocytes, the blocking effects of transplantation and progressor melanoma sera, and anti-tumor IgG antibody in melanoma patients and normal controls. Three of the nine melanoma patients possessed specific lymphocytotoxicity against melanoma cells, and 12 of the 34 controls possessed allogeneic lymphotoxicity against both the melanoma and fibroblast cells. Sera from the melanoma patients could block melanoma-specific systems, but, unlike the transplant sera, did not block allogeneic cell kill. Sera from all of the normals and eight of nine melanoma patients were unreactive to the melanoma and fibroblast cells in mixed agglutination assays; serum from the remaining melanoma patient reacted with both cell lines. Thus, the lymphocytes of both normal individuals and cancer patients frequently possess marked cytotoxicity against both cultured tumor cells and benign cells autogenous with the malignant cells. Furthermore, the cytotoxicity is not related to extraneous factors such as the presence of Ficoll-Hypaque macrophages, or infectious agents. The role of allogeneic immunity in testing for tumor immunity should be reassessed.

- 1463 RADIOIMMUNOASSAY FOR MOUSE MAMMARY TUMOR VIRUS-ASSOCIATED ANTIGEN. (E.) Lo Gerfo, P. (Coll. Phys. Surg., Columbia U., New York, N.Y.), G. Silverstein and J. Charney. *Surgery* 76(1):16-22, 1974.

Mouse mammary tumor virus (MTV) was isolated from Paris RIII/Haag milk and mouse mammary tumors, labeled with I^{125} , and rebanded in sucrose density gradients at 1.18 g/ml. Using the rebanded, labeled, intact particles, a radioimmunoassay was developed for the detection of antigens associated with MTV. An inhibition double-antibody assay was employed which allowed detection of the viral antigen in a 1:25,000 dilution of RIII milk. The quantity of this viral associated antigen (VAA) in Paris RIII and C57BL milk was then determined. The Paris RIII mice shed large amounts of viral antigen into their milk even at early lactations. Milk from a tumor-free colony of C57BL mice contained detectable amounts of VAA. Although inhibition curves from the milk of these animals were similar to those obtained with purified virus, this finding does not indicate that the mice shed intact virus into their milk. The levels of VAA in a group of C57BL mice which had been inoculated with MTV during the neonatal period correlated with the eventual development of mammary tumors, making it possible to predict which animals were susceptible to tumor development. Inhibition curves with Tween-treated virus and intact virus suggest that envelope antigen was being detected by the assay.

- 1464 TUMOR-SPECIFIC IMMUNITY IN 3-METHYLCHOLANTHRENE-INDUCED MURINE FIBROSARCOMAS. I. *IN VIVO* DEMONSTRATION OF IMMUNITY WITH THREE PREPARATIONS OF SOLUBLE ANTIGENS (E.) Brannen, G. E. (Johns Hopkins U. Sch. Med., Baltimore, Md.), J. S. Adams and G. W. Santos. *J Natl Cancer Inst* 53(1):165-175, 1974.

The *in vivo* response to soluble, syngeneic tumor-specific antigens (TSA) from 3-methylcholanthrene-induced fibrosarcomas was measured in male (BALB/c X DBA/2) F_1 (CD2 F_1) mice using the 3-, 24-, and 48-hr foot pad swelling (FPS) response. Mice immunized against the tumor by the surgical removal of a growing tumor had specific resistance to challenge with that tumor and specific 3-hr (Arthus) and 24- and 48-hr (delayed-hypersensitivity) foot pad responses to preparations containing viable, lyophilized (3M KCl extracts), homogenized, and frozen-thawed extracts, and sonication extracts of tumor cells. Specific FPS was seen in immunized mice with 3M KCl tumor extracts at protein concentrations of 200-10,000 μ g/ml. Protein concentrations of 5000 μ g/ml appeared to be optimal for testing. Mice given tumor cells had specific 3-hr FPS to KCl-prepared TSA 7 days after tumor transfer. All responses were negative after 28 days, when tumor diameters were greater than 1.5 cm. Surgical removal of the tumors in these mice restored the 3-, 24-, and 48-hr specific FPS within 24 hours.

- 1465 MODIFICATION BY PASSIVE IgM OF THE IMMUNE RESPONSE OF MICE TO A TUMOR ALLOGRAFT. (E.) Cantrell, J. L. (Oklahoma Med. Res. Fdn., Oklahoma City) and N. Kaliss. *J Natl Cancer Inst* 52(5):1619-1625, 1974.

Passive immunologic enhancement and rejection of tumor allografts and the induction of allohemagglutinins by the grafts were assayed in B K_s mice given an antitumor alloantiserum or its immunoglobulin M (IgM) fraction at the time of i.m. injection of tumor cells. Control groups did not receive passive antibody. Progressive tumor growth (enhancement) occurred only in the mice given whole antiserum. The growth of the grafts in mice given IgM, though exceeding that in the controls, was slight and transient. Mice were bled serially, and sera were used to determine hemagglutinin titers against the mouse strain of the tumor donor. Titers were detected by day 5 after sensitization in controls and mice given IgM, later in mice given whole antiserum. Sera were treated with 2-mercaptoethanol (2-Me) and titered for hemagglutinins. For the control mice, titers for the 5- and 8-day bleedings were obliterated by the 2-Me and were first detected at day 12; this indicated that IgM was the primary constituent of sera from the earliest bleedings. In the mice given whole antiserum, titers for days 12-19 disappeared and were first detected on day 22; this was consonant with the delayed response noted with passive whole antiserum. Sera from all bleedings of mice given IgM i.p. at the time of tumor inoculation exhibited titers despite treatment with 2-Me; apparently the IgM accelerated the IgG phase of the humoral response.

- 1466 CYTOSTATIC IMMUNOSUPPRESSIVE THERAPY, CHROMOSOME ABERRATIONS AND CARCINOGENIC ACTIVITY. (Ger.) Vormittag, W. (2nd Med. Clin., U. Vienna, Austria). *Wien Klin Wochenschr* 86(3): 69-75, 1974.

Chromosome studies were performed on peripheral lymphocyte cultures from 21 patients with chronic progressive polyarthritis before, during and after treatment with immunosuppressive agents. These patients consisted of 7 given procarbazine hydrochloride (250-500 mg/day i.v.; total of 4.0-6.5 g), 7 mannomustine (100 mg every other day i.v.; total of 0.65-1.0 g), one cyclophosphamide (150-200 mg/day p.o.; total of 2.9-19.6 g), and 6 azathioprin (25-100 mg/day p.o.; total of 16-144 g). Most of the patients continued to take other medication for arthritis (salicylates, indomethacin, cortisone derivatives, etc.) during the study. All the immunosuppressive agents studied, with the exception of azathioprin, produced significant increases in the percentage of metaphases with structural chromosome aberrations, primarily chromatid breaks by the end of the treatment period. The frequency with which these aberrations occurred was highest after treatment with procarbazine and endoxine; fewer aberrations were observed after mannomustine therapy. These findings correlate well with literature reports on the induction of tumors in experimental animals by these immunosuppressive agents. No definite evidence was obtained to indicate that any of the agent-induced chromosome anomalies preferentially occurred in any chromosome or group of chromosomes, and there was great individual variation in the number of aberrations within each treatment group, but some of the findings suggest that there are great individual differences in the ability to repair genetic damage. There is no evidence that chromosome aberrations observed in these patients were related to exposure to X-rays, other drugs, intercurrent viral infections, age, or sex.

- 1467 TRANSPLANTATION ANTIGENS (H-2) ON VIRALLY AND CHEMICALLY TRANSFORMED BALB/3T3 FIBROBLASTS IN CULTURE. (E.) Tsakraklides, E. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.), C. Smith, J. H. Kersey and R. A. Good. *J Natl Cancer Inst* 52(5):1499-1504, 1974.

Quantitative absorptions of monospecific and oligospecific H-2^d antisera were used to test differences in concentration of histocompatibility antigens on nontransformed BALB/3T3 (clone A31) mouse fibroblasts; on A31 fibroblasts transformed by Kirsten murine sarcoma virus (MSV), simian virus 40 (SV40), and 3-methylcholanthrene; and on spontaneously transformed A31 fibroblasts. Cells transformed spontaneously and by MSV showed increased H-2 concentration, whereas those transformed chemically and by SV40 had decreased H-2 antigen specificities. The findings correlated with the lower *in vivo* immunogenicity of cells transformed spontaneously and by MSV and with the higher immunogenicity of cells transformed chemically and by SV40. An inverse relationship between tumor-associated and histocompatibility antigens is suggested.

- 1468 WIDESPREAD NATURAL OCCURRENCE OF HIGH TITERS OF NEUTRALIZING ANTIBODIES TO A SPECIFIC CLASS OF ENDOGENOUS MOUSE TYPE-C VIRUS. (E.) Aaronson, S. A. (Natl. Cancer Inst., Bethesda, Md.) and J. R. Stephenson. *Proc Natl Acad Sci USA* 71(5):1957-1961, 1974.

To determine the natural host response to two biologically distinguishable endogenous type-C viruses contained in BALB/c mouse cells, sera from BALB/c mice were tested for virus-neutralizing activity. The sera were strikingly inhibitory to BALB:virus-2, but not to BALB:virus-1 or representative viruses of the Gross and Friend-Moloney-Rauscher (FMR) subgroups. Both BALB/c viruses were effectively neutralized by antisera against Gross but not by antisera against FMR. The inhibitory activity of normal BALB/c sera against BALB:virus-2 was attributable to natural antibodies directed against specific envelope antigen(s) of that virus. BALB/c sera effectively neutralized NZB-murine leukemia virus (MuLV), demonstrating the serologic relatedness of NZB-MuLV and BALB:virus-2. Sera from C58 mice had very high neutralizing titers against BALB:virus-2 and NZB-MuLV, but not against C58-MuLV or BALB:virus-1. Sera from a variety of mouse strains contained high antibody titers to BALB:virus-2 but not to BALB:virus-1 or C58-MuLV; only NIH sera lacked detectable neutralizing antibodies to BALB:virus-2. The differences in the natural immune response of mice to different endogenous viruses are due to factors other than differences in the immunogenicities of the viruses themselves. High titers of neutralizing antibodies against BALB:virus-2 and NZB-MuLV were present in NZB and BALB/c sera but not in the sera of NIH mice. The phenotypic properties of both BALB:virus-2 and NZB-MuLV were vertically transmitted as dominant genetic characteristics in F₁ hybrids of BALB/c or NZB strains with NIH mice.

- 1469 PURIFICATION AND CHEMICAL CHARACTERIZATION OF α -FETOPROTEIN FROM RAT AND MOUSE. (E.) Watabe, H. (Sch. Med., Hokkaido U., Sapporo, Japan). *Int J Cancer* 13(3):377-388, 1974.

α -Fetoprotein (AFP) was isolated from the serum and ascites fluid of Donryu rats bearing a transplantable ascites tumor, and mouse AFP was isolated from mouse fetal extracts. Horse antiserum to AFP was obtained after immunization with the antigen-antibody complex produced by mixing newborn rat serum with specific rabbit serum against rat AFP; the horse serum was monospecific for rat AFP and cross-reacted strongly with mouse AFP, but did not react with serum from other newborn mammals. Rat AFP was heterogeneous in disc electrophoresis and isoelectric focusing and had two different isoelectric points at pH 4.76 and 5.05. Mouse AFP was homogeneous when similarly analyzed. The molecular weight of both rat and mouse AFP was 70,000 as determined by gel electrophoresis in the presence of sodium dodecyl sulfate. The rat and mouse AFPs were also similar in their amino acid composition and had similar nitrogen, sulfur, and sugar contents.

- 470 BEHAVIOR OF INTERSTITIAL CELL TUMORS OF RODENTS *IN VIVO* AND *IN VITRO*. (Fr.) Courreau-Schneider, N. (Bicetre Hosp., Paris, France). *Bull Cancer (Paris)* 60(3):337-358, 1973.

In vivo studies were carried out in 7 lines of mouse tumors and one rat tumor of testicular origin which were maintained for several yr by serial passage in isogenic animals. Under various experimental conditions these tumors are remarkably stable. After isogenic implantation, almost all of the s.c. graft was rapidly destroyed. A new tumor nodule, originating from surviving tumor cells, formed after a delay of one to several months, depending on the line. Allografts were less successful as a result of strain-specific factors, but acceptance of the foreign graft was obtained by a first passage in allogeneic new borns whose immunological capacities were low, followed by implantation in young semi-isogenic hybrids. After this period of adaptation the tumors developed in adult allogenic hosts for several transfer generations. In allografts, as well as in isografts, the interstitial cell tumor of the WAG rat displayed the characteristics of the original tumor. *In vitro*, in organ and tissue culture, the morphology, synthetic capacities, and tumorigenic properties of malignant Leydig cells were maintained. A nodule formed after implantation into an isogenic host. A fibroblast-like cell line appeared after prolonged incubation of the WAG rat tumor, but only cultures containing epithelial-like cells with a glandular morphology produced a typical interstitial cell tumor.

- 471 SEROLOGICAL STUDIES OF NORMAL AND LEUKEMIC CATS IN A MULTIPLE-CASE LEUKEMIA CLUSTER. (E.) Cotter, S. M. (Angell Mem. Animal Hosp., Boston, Mass.), M. Essex and W. D. Hardy, Jr. *Cancer Res* 34(5):1061-1069, 1974.

Eleven cases of lymphoblastic leukemia and four cases of feline infectious peritonitis occurred in a private household population of 35 predominantly unrelated cats over a 39-month period. The study conducted on this population consisted of periodic physical examinations, hemograms, serological testing for feline leukemia virus group-specific antigens (gs) and for antibody to feline oncornavirus-associated cell membrane antigen (FOCMA). Leukemic household cats had a higher mean age and had been in the household longer than those that remained healthy. Six of nine leukemic cats were positive for FeLV (as were 9 of 10 leukemic cats living in other environments). Both the control and cluster household leukemic cats also had low geometric mean antibody titers to the FOCMA antigen (0.72 and 0.76 resp.). Healthy controls from outside the house were all negative for gs antigens and had a mean antibody titer of 1.66. Relatives of leukemic cats were no more likely to develop leukemia or become gs positive than relatives of healthy cats. Cats developing leukemia appear to be unable to produce or maintain a high FOCMA antibody titer. It is concluded that these data support the theory of horizontal transmission of feline leukemia virus.

- 1472 HUMAN IMMUNE RESPONSE TO ACTIVE IMMUNIZATION WITH RAUSCHER LEUKEMIA VIRUS. II. HUMORAL IMMUNITY. (E.) Hersh, E. M. (Dept. Developmental Therapeutics, U. Texas, Houston), M. G. Hanna, Jr., J. U. Gutterman, G. Mavligit, M. Yurconic, Jr. and C. R. Gschwind. *J Natl Cancer Inst* 53(2):327-333, 1974.

Thirteen patients with solid tumors and seven patients with leukemia were given 4 intradermal 100- μ g injections of formalin-inactivated Rauscher leukemia virus (RLV) at two-wk intervals. The patients were then followed for serum antibody response and *in vitro* lymphocyte blastogenic response to both RLV and an antigen extracted from RLV-infected and -transformed cells. Ten of the patients developed a significant antibody titer as measured by radioimmunoprecipitation. Among the responders, the mean titer, taken as the reciprocal of the highest serial twofold dilution yielding 50% virus precipitation, was approximately 1:354. Antibody first appeared two wk after immunization and reached a peak at eight wk. The antibody responses were most vigorous in patients with melanoma and in those receiving BCG plus chemotherapy; the responses were least vigorous in patients with other solid tumors or acute leukemia, and in those receiving chemotherapy without immunotherapy. There was an excellent correlation between the antibody response and the development of delayed hypersensitivity to the virus and between the antibody response and the *in vitro* lymphocyte blastogenic response to the antigen solubilized from RLV-infected cells. Extensive absorption studies indicated that sera from both immunized and nonimmunized subjects contained antimouse antibody. After *in vivo* absorption in mice, the patients' post-immunization sera retained antiviral activity.

- 1473 VIRUS-ASSOCIATED SURFACE ANTIGENS ON L CELLS AND MOLONEY LYMPHOMA CELLS. (E.) Fenyő, E. M. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), G. Grunder and E. Keln. *J Natl Cancer Inst* 52(3):743-751, 1974.

The A9 mouse fibroblast line, derived from the L-cell strain, lacks the enzyme hypoxanthine-guanine-phosphoribosyl transferase and carries a nonleukemogenic C-type virus which is morphologically indistinguishable from the murine leukemia viruses. The A9 cells possess on their surface the Moloney leukemia virus (MLV) envelope antigen (VEA), the L antigen, and the H-2k isoantigen complex. Antibodies with VEA specificity were induced in mice immunized with L cells. The L cells absorbed antiviral envelope antibodies from the anti-MLV serum but not the antibodies directed against the Moloney virus cell-surface antigen (MV-CSA). Absorption of the same serum with Moloney lymphoma cells, which carry both VEA and MV-CSA, was complete. Such Moloney lymphoma cells could not, however, remove the anti-L cell-surface activity from the anti-L serum. Anti-L serum reacted with NIH Swiss/3T3 cells and with the S⁺L⁻ (sarcoma positive, leukemia negative) cells, which indicates that the L antigen is an embryonic antigen.

- 1474 CIRRHOSIS AND MALIGNANT HEPATOMA IN α_1 -ANTITRYPSIN DEFICIENCY. (E.) Eriksson, S. (Gen. Hosp., Malmo, Sweden) and I. Hagerstrand. *Acta Med Scand* 195;451-458, 1974.

Over a 10-yr period, nine adults with severe α_1 -antitrypsin (AAT) deficiency (Pi^{ZZ}) and cirrhosis were examined clinically and given a variety of liver function and serologic tests. All patients were over 50 yr when cirrhosis was diagnosed. None had histories of icterus, neonatal hepatitis, or heavy drinking. All patients except one had sought medical attention because of portal hypertension in which ascites was the dominant clinical symptom. The disease was characterized by a rapidly progressive course with terminal complications in the form of coma or bleeding. Of the eight patients who died, six had malignant hepatoma which was multiple in two cases. One patient had manifest diabetes, three had close relatives with diabetes, and most had emphysema. Histologically typical PAS-positive inclusion bodies were present in all livers, while cholestatic features were not prominent. One patient had a normal albumin value, most had polyclonal hyper- γ -globulinemia, and two had high serum cholesterol values. The serum alkaline phosphatase activity was only moderately raised, while the prothrombin activity was low in all patients with portal hypertension. IgA, IgG, and IgM values were increased in most patients, IgM levels showing the largest increase. α_2 -Macroglobulin values were moderately raised and ceruloplasmin was slightly increased in most patients; haptoglobins tended to be low. Smooth muscle and mitochondrial antibody tests in four patients were negative, hepatitis-associated antigen could not be detected in seven patients, and α -fetoprotein was found in only one patient who had a malignant hepatoma. The pathogenic mechanism leading to cirrhosis in a minority (10%) of adult patients with the Pi^{ZZ} phenotype remains obscure.

- 1475 NEURAMINIDASE-INDUCED ENHANCEMENT OF TUMOR GROWTH IN MICE. (E.) Froese, G. (Manitoba Cancer Treatment Res. Fdn., Winnipeg, Canada), I. Berczi and A. H. Sehon. *J Natl Cancer Inst* 52(6):1905-1908, 1974.

The B16 melanoma (B16) was weakly immunogenic in C57BL/6J mice. B16 cells were killed by X-irradiation and injected s.c. into C57 mice prior to challenge with viable cells. The difference between the growth rate of tumors in treated and nontreated animals was not significant. However, when 0.075 mg of BCG was added to the inoculum, tumor growth was significantly retarded in the immunized mice; pre-immunization with BCG alone did not affect tumor growth. Using the microcytotoxicity test for the cytopathic capacity of lymph node cells from tumor-bearing animals, cytotoxic lymphocytes were demonstrated in tumor-bearing mice between 3-15 days after tumor implantation. Treatment of the X-ray-killed immunizing B16 cells with *Vibrio comma* neuraminidase resulted in enhanced growth of B16 tumors. Thus, B16 is a weakly antigenic tumor in C57 mice.

- 1476 ESCAPE OF SMALL NUMBERS OF ALLOGENEIC LYMPHOMA CELLS FROM IMMUNE SURVEILLANCE. (E.) Bonmassar, E. (Lab. Tumor Immunol. Chemother., U. Perugia, Italy), E. Menconi, A. Goldin and G. Cudkowicz. *J Natl Cancer Inst* 53(2):475-479, 1974.

Radiation-induced lymphoma cells from B10.A mice (LAF-17), B10 mice (S1033 and LBF-23), and B10.129 (5M) mice (L5MF-22) were inoculated i.v. or i.p. into congenic-resistant hosts. Mice of these lines share the genetic background of B10 but differ at a chromosome segment of linkage group IX, which includes the major histocompatibility complex or subregions of it. Relatively small grafts (10^5 cells) consistently escaped immune surveillance and grew progressively, whereas larger grafts (10^6 - 10^7 cells) were rejected. The mechanism of this dilution escape was investigated using B10.A lymphoma (H-2^a) transplanted into H-2K-Ir incompatible B10.A(5R) mice (H-2^d). The recipients were subjected to splenectomy, adoptive or active immunization before and after tumor grafting, and various antitumor and immunosuppressive treatments. The tumor cells were used after either serial syngeneic or allogeneic passages under conditions of dilution escape. The results did not support the hypothesis that active enhancing responses by the host, antigen simplification of tumor cells, and reduced immunosensitivity of lymphoma grafts influence dilution escape. The hypothesis of creeping tumor growth to a population size overwhelming the host's immune defenses was also inadequate to account for all experimental findings. The data indicated that factors depressing antilymphoma allograft reactivity were associated with tumor cells. Thus, dilution escape may be the result of a nonspecific inhibition of antilymphoma allograft reactions before the initially small tumor cell population reaches the size required to be immunogenic.

- 1477 HL-A AND ABO ANTIGENS AND MALIGNANT MELANOMA: A STUDY OF 212 CASES. (E.) Lamm, L. U. (U. Hosp. Aarhus, Denmark), F. Kissmeyer-Neilsen, K. E. Kjerbye, B. Mogensen and N. C. Petersen. *Cancer* 33(5):1458-1461, 1974.

Two hundred and twelve melanoma patients, including 38 prospective and 174 retrospective cases, were ABO and HL-A typed, and the results were compared with those obtained from a sample of 562 healthy controls. The phenotype frequencies within the ABO system were identical in the patients and controls. A lower frequency of HL-A7 (significant at the 5% level) was observed in the melanoma patients. Furthermore, significant deviations from the controls were observed in the following patient subgroups: the females showed a deficiency of HL-A7; and patients with chances of 5-yr corrected survival rates of 0-19% and 20-79% showed surpluses of HL-A1 and W19, respectively. However, although statistically significant, the deviations should at the present time be considered fortuitous in that roughly 200 comparisons were made. Thus, the investigation did not shed any light on the etiology of malignant melanoma or the prognosis of the patients.

1478 SERUM AND IMMUNOLOGICAL STUDIES IN PATIENTS WITH LYMPHOMAS. XIII. INVESTIGATION OF CELLULAR IMMUNITY INDUCED BY SPECIFIC AND NONSPECIFIC STIMULANTS. (Sp.) Giraudo Conesa, L. C. (Inst. Hematol. Res., Natl. Acad. Med., Buenos Aires, Argentina), M. Braun, A. Pavlovsky and A. E. Bachmann. *Sangre* 18(3):305-312, 1973.

The effect of phytohemagglutinin (PHA), extracts from neoplastic lymph nodes, and lymphoid cells from GH7 and LDLT cell lines on blast cell formation was studied in peripheral lymphocyte cultures from 11 patients (5 females and 6 males, aged 14-59 yr) with Hodgkin's disease, 23 patients (9 females and 14 males, aged 16-75 yr) with lymphosarcoma and 34 hematologically normal controls (16 females and 18 males, aged 19-41 yr). The mean percentage of PHA-induced blast cell formation was 50% in cultures from patients with Hodgkin's disease, 47% in those from patients with lymphosarcoma and 65% in those from controls. Among patients with Hodgkin's disease the greatest suppression of lymphocyte transformation control occurred in cultures from patients with the most severe histological forms of the disease. Autoradiography of cultures from 8 patients (4 with Hodgkin's disease and 4 with lymphosarcoma) to which pathological homologous cellular antigen had been added demonstrated that appreciable nuclear incorporation of ^3H -thymidine occurred in only 2 cases. This labeling was detected in 1.7% and 0.66% of the blast-like cells, resp. in cultures from 2 patients with Hodgkin's disease. Since virus-like particles have previously been detected in LDLT cells, this stimulation could be caused by viral antigenic determinants in the extracts. It is unlikely that stimulation could have been caused by antigenic differences in the HL-A system since control cultures gave negative results with these extracts.

1479 HEPATOCELLULAR LOCALIZATION OF FETAL ANTIGENS DURING INDUCTION OF RAT LIVER TUMORS BY 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE. (E.) Cauchi, M. N. (Monash U. Med. Sch., Melbourne, Australia), J. B. W. Halley, M. G. Irving and J. F. Williams. *Cancer Res* 34(8):1808-1812, 1974.

The appearance of embryonic-type antigens prior to obvious neoplastic transformation of Wistar rat liver following the ingestion of 3'-methyl-4-dimethylamino-benzene (0.06%) was studied with antisera against fetal rat serum (anti- α -fetoprotein) and fetal liver antigen. Within 20 days of administration of carcinogen, α -fetoprotein was detected in the circulation by means of gel diffusion. By 40 days, both α -fetoprotein and fetal liver antigen could be localized by indirect immunofluorescent techniques in the livers of treated animals but not in control rats. The staining was confined to small patches which increased in size and became confluent with frankly neoplastic lesions. There was no evidence of antibody production to fetal antigens, but autoantibodies reacting with cell nuclei and with liver cell cytoplasm were detected by immunofluorescent techniques.

1480 DETECTION OF MAREK'S DISEASE VIRAL ANTIGENS WITH THE AID OF IMMUNE SERA CONJUGATED TO PEROXIDASE. (Fr.) Cauchy, L. (Natl. Inst. Agricultural Res., Monnaie, France). *C R Acad Sci [D] (Paris)* 277(19):2093-2096, 1973.

Localization of sites of viral replication in Marek's disease in chickens was studied with the aid of direct or indirect immunofluorescence. Two viruses were used: (1) a highly pathogenic virus isolated from chicken (JM strain); 2) a virus isolated from turkey, which is not pathogenic to chicken but which is used as a vaccine throughout the world (HVT-FC 126 strain). Sera were obtained from SPF chickens hyperimmunized or nonhyperimmunized with Marek's disease virus. Immune sera thus obtained were titrated by the techniques of precipitation in agar and indirect immunofluorescence. Sera of chickens possessing specific Marek's disease globulins were conjugated to peroxidase and were used for detection of antigens associated with virus replication. Marking of microphages in infected cultures of chicken kidney permitted the attachment of specific immune sera to be revealed by the brown or yellow-brown staining of oxidation derivatives of diaminobenzidine. Staining varied with cells, but no differences were observed with the different stains of virus used. The procedure of double marking (direct immunoperoxidase and indirect immunofluorescence) revealed that cells specifically colored by diaminobenzidine are also fluorescent in UV light despite the masking which results from the brown staining. The antigenic sites are identical to those revealed by immunofluorescence applied to Marek's disease. No antigen formation is observed outside of the focus of cell lysis following viral replication. Similar results were previously obtained with this technique in infections of the *Herpes* virus type.

1481 SERUM PROTEIN CHANGES IN THE DEVELOPMENT OF A TRANSPLANTABLE MURINE ASCITES MYELOID LEUKEMIA. (E.) Merino, F. (Dept. Exp. Med., Venezuelan Inst. Sci. Invest., Caracas). *Oncology* 29(4):283-293, 1974.

Hypoalbuminemia and increase of α -, β -, and γ -globulins in the serum proteins of inbred C51B1/6 and C3H/HeJ mice bearing a myeloid leukemia are reported. These changes are not specifically related to tumor growth and were gradually produced according to the different generation transplants of the tumor. An immunoglobulin fraction could be eluted from the tumor cells by treatment with a nonionic detergent. It is possible that this increase of the serum γ -globulin may be related to the immunological reaction of the host to the tumor cells. An alternative hypothesis would be that with a greater number of transplantable cells a simultaneous transfer of a greater concentration of tumor-associated immunoglobulins would take place and that these contribute to the increase of the serum γ -globulin. The search for serum proteins antigenically different from those of normal serum was unsuccessful.

- 1482 IMMUNE SURVEILLANCE AND TUMOR DISSEMINATION: *IN VITRO* COMPARISON OF THE B16 MELANOMA IN PRIMARY AND METASTATIC FORM. (E.) Goldman, L. I. (Temple U., Philadelphia, Pa.), B. A. Flaxman, G. Wernick and J. B. Zabriskie. *Surgery* 76(1):50-56, 1974.

Young C57Bl6 mice were inoculated s.c. with B16 melanoma cells, after which a comparison was made between the B16 melanoma in s.c. "primary" form and the pulmonary metastases which developed spontaneously following amputation of the primary site (the hind limb). The primary tumors were always nonpigmented while the metastases were invariably black. Ultrastructural examination indicated that this difference was due to the presence of melanosomes and premelanosomes in the metastases, compared with the absence of pigment production in the premelanosomes of the primary cells. The primary tumor cells induced a higher *in vitro* blastogenic response than the secondary cells in a mixed lymphocyte-tumor cell reaction assay. Using this assay, immunization could be detected following pretreatment with live secondary cells. Live primary cells produced an immunologically detectable response only when larger doses of mitomycin-treated cells were used as an immunogen or when simultaneous comparisons were made between experimental and control cultures. Thus, at least two biologically distinct cell populations were observed.

- 1483 ANTIBODIES TO HERPESVIRUS TYPE 2 IN BREAST CANCER AND CERVICAL CANCER PATIENTS. (E.) Adam, E. (Dept. Virol., Baylor Coll. Med., Houston, Tex.), E. K. Sanders, J. L. Melnick, A. H. Levy and W. E. Rawls. *Cancer* 33(1):147-152, 1974.

Antibody titers to herpesvirus types 1 and 2 were measured in the sera from 43 patients with breast cancer, 50 patients with cervical cancer, and 186 women without malignant or gynecologic disease. All subjects were lower socioeconomic class Negroes. The three groups were compared with respect to age at first intercourse, age at first marriage, age at first pregnancy, number of marriages, number of sex partners, and number of live births. The breast cancer patients differed significantly from the other women only in being slightly older at first marriage. The distribution of antibodies to the herpesviruses was similar for the breast cancer patients and the control women. However, the antibody distribution in the breast cancer patients differed from that in the cervical cancer patients in that there was an increased occurrence of antibodies to herpesvirus type 2 among the latter group. In addition, the breast cancer patients and controls who experienced first sexual intercourse, first pregnancy, and first marriage after ages 15 and 16 years, respectively, had significantly fewer antibodies to type 2 virus than the cervical cancer patients who had these experiences at similar ages. These data support the view that the high frequency of herpesvirus type 2 antibodies among cervical cancer patients is not due solely to increased sexual promiscuousness in this group of women.

- 1484 ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY TO A SYNGENEIC GROSS VIRUS-INDUCED LYMPHOMA. (E.) Ortiz de Landazuri, M. (U. California Sch. Med., Los Angeles), E. Kedar and J. L. Fahey. *J Natl Cancer Inst* 52(1):147-152, 1974.

Normal W/Fu rat lymphoid cells exerted a specific cytotoxic effect on syngeneic (C58NT)D tumor cells in the presence of sera from W/Fu rats immune to Gross virus-induced lymphoma. The antibody-dependent cellular cytotoxicity (ADCC) reaction did not produce detectable release of nonspecific cytotoxic substances, was not diminished by inhibitors of complement, and was more sensitive in detecting antibodies than a test requiring the external addition of complement. After a single immunization (1×10^6 tumor cells s.c.), activity began at day 10 and was maximum about 30-40 days after tumor inoculation. ADCC activity was greatest with peripheral blood lymphocytes, intermediate with spleen cells, and only slightly positive with lymph node cells. Thymus and bone marrow were always negative. There was no correlation between the capacity to mediate ADCC and the ability to bind to antibody-coated target cell (e.g., form rosettes with antibody-sensitized erythrocytes) in the various normal lymphoid organs. Fractionation on G-200 Sephadex and blocking of serum activity by minute amounts of rabbit antirat IgG serum indicated that the activity of the sera is due to 7S antibodies.

- 1485 T LYMPHOCYTES IN BLADDER AND PROSTATIC CANCER PATIENTS. (E.) Catalana, W. J. (Johns Hopkins Hosp., Baltimore, Md.), C. Potvin and P. B. Chretien. *J Urol* 112(3):378-382, 1974.

To determine whether impaired cellular immune responsiveness in urologic cancer patients is related to a reduction in the number of T lymphocytes, circulating levels of T rosette-forming lymphocytes were measured in 21 patients with bladder cancer and 25 patients with prostatic cancer. The results were compared with those found in 83 age-matched healthy controls. The T lymphocyte levels were significantly reduced in the peripheral blood of both groups of cancer patients compared with the controls. The T cell levels appeared to correlate inversely with tumor stage in the bladder cancer patients but not in the prostatic cancer patients. A possible consequence of reduced numbers of circulating T lymphocytes would be a diminution in tumor-inhibiting (T cell) influences and a corresponding relative enhancement of blocking (B cell) influences, a condition which would favor tumor proliferation.

- 1486 THE MIGRATION OF LYMPHOID CELLS IN MALIGNANT DISEASE. (E.) Stein-Werblowsky, R. (Roy. Vet. Coll., London, England). *Experientia* 30(4):422-423, 1974.

Transplantable rat tumors were grafted into the flanks of adult Wistar rats. After 12 days, segments of the tumor were excised and divided into three portions: one portion was grafted into the

non-tumor-bearing flank of the donor; one portion was sealed in a plastic millipore chamber and placed in the abdominal cavity of the donor; and one portion was sealed into a millipore chamber along with packed rat lymphoid cells and placed in the abdominal cavity of the donor. After 7 days, the chambers were removed and the tumor fragments taken out and implanted s.c. into weanling Wistar rats. Control nonmalignant homografts were rejected or destroyed within 10-13 days following a progressive accumulation of mononuclear cells at the graft site. A similar reaction took place at the site of implantation of the malignant grafts and there was a blastic response in the regional node. However, the peritumoral white cell reaction gradually subsided and disappeared by the 6th day. The tumor fragments in the millipore chambers remained viable but lost their viability and transplantability when exposed to lymph node cells, particularly the lymphocytes of the tumor-bearing host. Close contact with the tumor conferred some cytotoxicity to nonsensitized lymphocytes. Cytotoxicity was not affected by serum factors penetrating the pores of the chamber.

- 1487 A DIRECT RELATIONSHIP BETWEEN IMMUNE COMPETENCE AND THE SUBCUTANEOUS GROWTH RATE OF A MALIGNANT MURINE LUNG TUMOR. (E.) Yuhas, J. M. (Oak Ridge Natl. Lab., Tenn.), N. H. Pazmino, J. O. Proctor and R. E. Toya. *Cancer Res* 34(4): 722-728, 1974.

The transplantability and growth of a malignant alveolar cell carcinoma of BALB/C mouse lung was studied in syngeneic hosts. In untreated mice, the cancer can be established with fewer than 100 cells and grows with a volume doubling time of 3.1 days. Total-body irradiation of the host with 500 R 2 hr prior to s.c. inoculation with tumor cells does not affect the transplantability of the tumor but significantly suppresses its growth rate. This suppression of the growth rate is not associated with a generalized body wt loss and cannot be induced by localized irradiation. Injection of hydrocortisone acetate (5 mg) prior to tumor inoculation or use of immunologically crippled senescent hosts yields a similar suppression. Further, suppression of the growth rate of the cancer by total-body irradiation can be reversed by transplantation of syngeneic lymph node or spleen cells immediately after irradiation. It is unlikely that this reduced growth rate of s.c. tumors in immunosuppressed hosts results from inhibition of immunological reactions which stimulate growth or from a preferential loss of "blocking" factors, since metastasis proceeds more rapidly in immunosuppressed hosts and splenectomy does not slow the growth of the s.c. tumor.

- 1488 DEVELOPMENT OF RETICULUM CELL SARCOMA DURING CYCLOPHOSPHAMIDE THERAPY. (E.) Tannenbaum, H. (Harvard Med. Sch., Boston, Mass.) and P. H. Schur. *Arthritis Rheum* 17(1):15-18, 1974.

A 55-yr-old white female was admitted to the hos-

pital with a clinical picture of deforming rheumatoid arthritis associated with serologic and histologic evidence of systemic lupus erythematosus. A year and a half later, she was started on cyclophosphamide (50 mg/day) and on prednisone (20 mg every other day). Two months later, the amount of cyclophosphamide was raised to 100 mg alternating with 50 mg every other day. Thirteen months later, the patient complained of thoracic pain. A deep large mass excised from the thoracic spinal region was microscopically diagnosed as a reticulum cell sarcoma. Although it is not possible to causally relate the tumor seen in this patient to the cyclophosphamide administered, therapy with immunosuppressive agents in humans should be used with great caution.

- 1489 THE IMMUNE RESPONSE TO PRIMARY MOLONEY SARCOMA VIRUS TUMORS IN BALB/c MICE: CELLULAR AND HUMORAL ACTIVITY OF LONG-TERM REGRESSORS. (E.) Lamon, E. W. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), B. Andersson, H. Wigzell, E. M. Fenyö and E. Klein. *Int J Cancer* 13(1):91-104, 1974.

Adult BALB/c mice injected i.m. with Moloney sarcoma virus (MSV) developed local tumors at the site of inoculation; these tumors spontaneously regressed within 20-25 days after inoculation. The lymphocytes and sera from the long-term regressor animals were examined *in vitro* for specific activity against Moloney leukemia virus (MLV) determined antigen(s). Activity of the immune lymphocytes from these animals against MLV-antigen-bearing target cells was dependent on the presence of B lymphocytes. The immune B cells were active only against target cells bearing the MLV antigen(s), not against the control target cells which were MLV-antigen negative. Both anti-T and anti-Ig columns contained antigen antibody complexes, but only the latter retained the active cells. Thus, such anti-Ig columns, in the mouse system, primarily remove cells by surface Ig and not by Fc-binding surface receptors. To investigate the possible mechanisms of action of the immune B cells, sera were tested for their ability to stimulate normal syngeneic lymphocytes to be active against the target cells. These antisera stimulated normal unfractionated and T-deprived cells to reduce the target cell numbers. This effect was not found with normal T lymphocytes.

- 1490 ASPECTS OF EPSTEIN-BARR VIRUS INFECTION IN CHILDHOOD. (E.) Sutton, R. N. P. (King's Coll. Hosp. Med. Sch., London, England), S. D. Marston, E. J. P. Almond and R. T. D. Emond. *Arch Dis Child* 49(4):102-106, 1974.

Antibodies to Epstein-Barr (EB) virus capsid antigen and EB virus complement fixing antibodies were estimated in sera from 23 children and 27 young adults with infectious mononucleosis, and in 79 control patients. Anomalous results, in which the EB virus antibody pattern suggested active infection although heterophile antibodies and/or abnormal white blood

cells were absent, were observed in sera from patients of all ages but the majority were aged five yr or less. The proportion of sera with EB virus antibodies increased throughout childhood, suggesting that infection with this virus is relatively frequent in this age group and may often be unrecognized. Such infections may not be innocuous in view of the evidence that young adults with subclinical EB infection develop antibodies to smooth muscle; the relation of such antibodies to liver damage and to malignant disease is well recognized.

1491 HISTOLOGIC DIFFERENCES IN BREAST CARCINOMA OF JAPANESE AND AMERICAN WOMEN. (E.)

Chabon, A. B. (Beth Israel Med. Ctr., New York, N.Y.), S. Takeuchi and S. C. Sommers. *Cancer* 33(6):1577-1579, 1974.

Breast cancers in 104 Japanese women and 100 American women were compared histologically. In both series the most common histologic type was the infiltrating duct cell carcinoma. Medullary carcinomas were more common in Japanese women. The two groups did not differ significantly in nuclear grade of cancer cells or in epithelial proliferative changes in ducts of noninvolved breast tissue. The major histologic difference was the increased lymphocytic infiltration around the Japanese breast cancers: 52% of the Japanese series had marked infiltration compared with 27% of the American series ($p < 0.01$). This finding confirms previous studies and is suggestive of greater host resistance to breast cancer among Japanese women.

1492 RELATIONSHIP OF CARCINOEMBRYONIC ANTIGEN TO BLOOD SUBSTANCES A AND i: EVIDENCE THAT THE ANTIGENIC SITES ARE ON DIFFERENT MOLECULES. (E.)

Cooper, A. G. (Tufts U. Sch. Med., Boston, Mass.), M. C. Brown, M. E. Kirch and A. H. Rule. *J Immunol* 113(4):1246-1251, 1974.

Extracts of human colon carcinomas were assayed for the presence of blood group substance A and i activities using an automated quantitative hemagglutination-inhibition system. Carcinoembryonic antigen (CEA) activity was simultaneously assayed by radioimmunoassay. Isoelectric focussing of a perchloric acid tumor extract containing all three antigen activities indicated a similar pK_1 for the three antigens. However, A- or i-specific affinity gel adsorption experiments showed that only the corresponding blood group antigen activity was removed from tumor extracts. CEA activity remained essentially the same after adsorption by these gels. Significant blood group activity could not be demonstrated in preparations of highly purified CEA or in CEA from which N-acetylneuraminic acid and fucose had been removed. Conversely, CEA activity was absent from preparations of purified blood group antigens and could not be unmasked by removal of the immunodominant β -galactose of the i antigen with β -galactosidase. These data provide evidence that the antigenic sites for CEA and blood group A and i antigens are located on different molecules in colon carcinoma extracts.

1493 ISOLATION OF TUMOR-LOCALIZING ANTIBODIES WITH IMMUNOABSORBENTS. II. ISOLATION OF HETEROLOGOUS ANTIBODIES TO A MOUSE TUMOR INDUCED BY UV IRRADIATION. (Ger.)

Teichmann, B. (Ctr. Inst. Cancer Res., Berlin-Buch, Germany) and R. Vogt. *Arch Geschwulstforsch* 42(3):285-297, 1974.

Over an eight-month period, rabbits were immunized with an extract obtained by homogenization and low-speed centrifugation of a mouse sarcoma originally obtained by exposure of C17 x AKR mice to UV radiation. This tumor was then transplanted into male mice and proved to be antigenic in an isologous system. In addition to reacting with extracts from these tumors, serum from immunized rabbits also reacted with mouse serum and plasma and extracts from mouse liver, lungs, heart, kidney, and spleen. After concentration by precipitation with ammonium sulfate, rabbit immunoglobulins were reacted stepwise with immunoabsorbents specific for normal mouse serum and tissues. The base used in preparing these immunoabsorbents was cellulose-m-aminobenzoxy methyl ether which contained one diazotizable group per 47 glucose units of the cellulose derivative. Since Ochterlony tests and immunoelectrophoresis demonstrated that all antibodies for normal tissues had not been removed, γ -globulins from this preparation were isolated by two successive gel filtrations through Sephadex G-200. These pure γ -globulins were found to react only with mouse tumor extracts. These experiments provide the basis for obtaining heterologous, tumor-localizing antibodies for human tumors.

1494 CHANGES IN THE NUCLEAR MEMBRANE SURFACE FOLLOWING TRANSFORMATION OF CHICK EMBRYO FIBROBLASTS BY ROUS SARCOMA VIRUS: THE EFFECT OF CAMPTOTHECIN. (E.)

Spataro, A. C. (U. Rochester Sch. Med. Dentistry, New York), H. R. Morgan and H. B. Bosmann. *Biochem Pharmacol* 23(13):1921-1926, 1974.

Primary cultures of chick embryo fibroblasts (CEF) were infected with the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) and were harvested in 0.44 M sucrose, 3.3 mM CaCl_2 after transformation. The electrophoretic mobility of the nuclei isolated from these cells was then determined. The CEF cell nuclei had a much higher net negative electrophoretic mobility than rat liver sucrose, CaCl_2 nuclei, transformation of the CEF cells by SR-RSV caused a significant elevation in the net electrophoretic mobility of the isolated sucrose, CaCl_2 nuclei, and both the CEF and SR-RSV-CEF sucrose, CaCl_2 nuclei had large numbers of electrons per particle surface. After treatment of the nuclei with neuraminidase, the electrophoretic mobilities of SR-RSV-CEF and CEF nuclei were the same, whereas hyaluronidase-treated nuclei had significantly decreased mobilities, the mobility of the isolated SR-RSV-CEF nuclei was higher than that of the CEF nuclei after hyaluronidase treatment. Incubation of the whole cells with 100 μg camptothecin had no effect on the electrophoretic mobility of the "normal" or transformed nuclei. The data indicate that, like the surface plasma membrane, the surface of a subcellular par-

ticle is altered in oncogenically transformed cells. Thus, the viral genome alters the host cell synthesis and degradation of both plasma membrane components and nuclear membrane and possibly other subcellular particle surfaces.

- 1495 THE DELAYED AND LASTING REJECTION OF MAMMARY ADENOCARCINOMA CELL TUMORS IN DBA/2 MICE WITH USE OF KILLED *Bordetella pertussis*. (E.) Likhite, V. V. (Harvard Med. Unit, Boston, Mass.). *Cancer Res* 34(5):1027-1030, 1974.

Transplanted mammary adenocarcinoma cells form solid tumors when injected s.c. in syngeneic DBA/2 mice. If approximately 26×10^9 killed *Bordetella pertussis* organisms are admixed with the tumor cells prior to inoculation, the tumors undergo a rapid and permanent rejection that begins two wk later. The protection conferred is lasting and remains specific for the antigenic cell line of tumor originally used. The nature of the permanent remission strongly suggests that the tumors were rejected as the consequence of an immune response. Histological sections of rejecting tumors reveal an infiltration of macrophages, lymphocytes, and numerous mast cells. The possible role of mast cells in tumor rejection is discussed.

- 1496 AN IMMUNOSUPPRESSIVE PEPTIDE FRACTION IN THE SERUM OF CANCER PATIENTS. (E.) Glasgow, A. H. (Dept. Surg., Boston U., Mass.), J. O. Menzoian, R. B. Nimberg, S. R. Cooperband, K. Schmid and J. A. Mannick. *Surgery* 76(1):35-42, 1974.

Phytohemagglutinin stimulation of human peripheral lymphocytes *in vitro* was used to measure the immunosuppressive activity of sera from hospitalized patients with solid tumors, hospitalized noncancer patients, and normal volunteers. The immunosuppressive activity of the sera from the cancer patients was 5-10 times greater than that of the sera from the noncancer patients and volunteers. This difference could be related to the presence of a considerable amount of immunosuppressive activity in protein peaks I and II of the cancer sera. The sera were then fractionated by DEAE ion exchange chromatography. A peptide fraction was obtained from the first DEAE protein peak by acidification and diafiltration. The immunosuppressive activity of the cancer sera, as represented by the immunosuppressive activity of peak I, could be reduced by removing from it a peptide which contained immunosuppressive activity. Thus, in both the cancer and normal sera, it is the peptide fraction which is responsible for the immunosuppressive activity.

- 1497 ESTERASE ACTIVITY OF CARCINOEMBRYONIC ANTIGEN. (E.) Munjal, D. (Boston City Hosp., Mass.) and N. Zamcheck. *Cancer Res* 34(8):2137-2141, 1974.

Purified carcinoembryonic antigens extracted with and without perchloric acid from hepatic metastases of

adenocarcinoma of the colon exhibited 6.9 and 10.4% of activity of carboxylesterase (on a rate basis). Activity was measured by hydrolysis of chromogenic substrates. No adenosine triphosphatase (Ca^{2+} and Mg^{2+} activated), chymotrypsin, carboxypeptidase A, cystine aminopeptidase, acid phosphatase, alkaline phosphatase, sulfatase, or glucuronidase activities were found associated with carcinoembryonic antigen. The esterase activity may help regulate cell division.

- 1498 ACTIVATION OF SUPPRESSOR T CELLS BY TUMOUR CELLS AND SPECIFIC ANTIBODY. (E.) Gershon, R. K. (Yale U. Sch. Med., New Haven, Conn.), M. B. Mokyr and M. S. Mitchell. *Nature* 250(5467):594-596, 1974.

Experiments were performed to determine whether suppressor T cells are involved in passive enhancement of tumor growth. More than 30% of the macrophages from sham-thymectomized, lethally-irradiated bone-marrow reconstituted mice C57BL/6, which were otherwise untreated, attached L-1210 tumor cells in the presence of cytophilic antibody. If these mice were treated with viable or mitomycin C-killed tumor cells plus isoantibody ten days before assay, less than 10% of the macrophages attached tumor cells. Pretreatment with isoantibody and L-1210 did not alter the capacity to attach L-1210 cells in the thymus-deprived mice which attached tumor cells in a way indistinguishable from those of the sham-thymectomized untreated ('normal') animals. The data demonstrate the thymus dependence of the ability of antibody and tumor cells, perhaps acting as complexes, to suppress the binding of tumor cells to macrophages in the presence of cytophilic antibody.

- 1499 ANTIGEN DISTRIBUTION IN AKR MOUSE LEUKEMIA. (E.) Ram, M. D. (Inst. Path., Case Western Reserve U., Cleveland, Ohio), R. R. Kohn and D. Novak. *J Natl Cancer Inst* 52(5):1505-1514, 1974.

Antigen distribution was studied by use of ^{51}Cr -labeled sheep RBC and ^{131}I -labeled aggregated human serum albumin in AKR mice with advanced leukemia and in controls. The spleens of leukemic mice had a poor uptake of the antigen as compared with that in the controls, whereas the liver in the leukemic mice showed a variable uptake depending on the degree of leukemic involvement. The distribution of carbon particles in the two groups of mice was studied histologically after i.v. injection of colloidal carbon given late in the leukemic process and also before the onset of leukemia. Uptake of the carbon by the leukemic spleens and livers was poor, which confirmed the isotopic results. Also, preexisting reticuloendothelial cells were dispersed in the leukemic organs. These results indicate that impaired antigen distribution may account, in part, for the lack of antibody-forming cells in the late AKR leukemia. Leukemia cells presumably make the reticuloendothelial cells and macrophages inaccessible to the antigen, or inhibit their uptake of the antigen.

- 1500 FETAL-LEUKEMIC ANTIGEN OF CHICKEN BLOOD CELLS. (E.) Teplitz, R. L. (City Hope Natl. Med. Ctr., Duarte, Calif.), B. G. Sanders, A. M. Brodetsky, H. Fung and K. L. Wiley. *Cancer Res* 34(5):1049-1053, 1974.

A membrane antigen on the RBC of chickens present at the time of hatching disappears during development of the animal and reappears in adult avian myeloblastosis virus-induced leukemic chickens. A relationship between the membrane antigen and viral product was ruled out with serological studies. The antigen is expressed in normal adult chickens on several tissues, especially on cells (presumptive erythroblasts) localized to the bone marrow. Possible modes of regulation explaining the reappearance of the antigen are discussed, with preference given to the hypothesis that the antigen is expressed during cell maturation or differentiation.

- 1501 MODIFIED RADIOIMMUNOASSAY FOR MURINE SARCOMA-LEUKEMIA VIRUS GROUP-SPECIFIC ANTIGEN. (E.) Spira, G. (Baylor Coll. Med., Houston, Tex.), N. Biswal and G. R. Dreesman. *Appl Microbiol* 28(2):239-244, 1974.

Iodination of disrupted Moloney strain murine sarcoma-leukemia virus resulted in labeled group-specific (gs) protein which was subsequently purified on an iso-electrofocusing column. This iodinated purified gs antigen, prepared from a relatively small quantity of purified virus, was used in a radioimmunoassay. A radioimmunoassay inhibition method was developed so that antibody specific for mammalian C-type gs antigen could be measured in undiluted or low dilutions of test serum without altering the known reactions of the test. The gs antigen isolated from purified moloney strain murine sarcoma-leukemia virus has an isoelectric point (pH 5.95) which is significantly lower than that reported for other murine leukemia viruses.

- 1502 SYNTHESIS OF α -FETOPROTEIN BY MEMBRANE-BOUND POLYSOMES OF RAT ASCITES HEPATOMA CELLS. (E.) Kanai, K. (Fac. Med., U. Tokyo, Japan). Y. Endo, T. Oda and N. Tanaka. *Cancer Res* 34(8):1813-1815, 1974.

The incorporation of ^{14}C -leucine into α -fetoprotein (AFP) *in vitro* was studied using free and membrane-bound polysomes from AFP-producing AH-66 rat ascites hepatoma cells. In both free and membrane-bound ribosomes, the uptake of radioactivity increased rapidly during the first 20 min, reaching a plateau after about 40 min. Free polysomes prepared without sodium deoxycholate treatment were more active than membrane-bound polysomes treated with sodium deoxycholate. When EDTA was added, the radioactivity of the supernatant increased by about 50% with both free and bound polysomes. The relative amount of AFP released from the polysomes was not altered by EDTA. Membrane-bound polysomes prepared from rat liver also incorporated ^{14}C -leucine into serum albumin,

whereas free polysomes did not. The incorporation of ^{14}C -leucine into the AFP fraction by membrane-bound polysomes was about 20-90 times higher than that by free polysomes. Thus, AFP is synthesized mainly on membrane bound-polysomes in rat ascites hepatoma cells, suggesting that AFP in hepatomas is an "excretory protein" such as serum albumin.

- 1503 SEROLOGICAL ANALYSIS OF IMMUNE RESPONSE TO FRIEND VIRUS-INDUCED LEUKEMIA. (E.) Ting, C.-C. (Natl. Cancer Inst., Bethesda, Md.) and R. B. Herberman. *Cancer Res* 34(7):1676-1683, 1974.

Serological analysis of the antigenic specificities expressed on Friend virus-induced leukemia cells was performed with the isotopic antiglobulin technique. The antisera were produced by syngeneic immunization of C57BL/6 mice with Friend virus-induced leukemia FBL-3. At least three antigenic specificities could be defined by these antisera: one was type specific for Friend virus-induced leukemia; the second was a broadly cross-reactive antigen of fetal nature; and the third was a group-specific (Friend-Moloney-Rauscher) antigen, which can be further separated into FM antigen (a common antigen between Friend and Moloney virus-induced leukemias) and FR antigen (a common antigen between Friend and Rauscher virus-induced leukemias).

- 1504 COLPOSCOPIC AND CYTOLOGIC EVALUATION OF WOMEN UNDERGOING IMMUNOSUPPRESSIVE THERAPY. (E.) Donohue, L. R. (Dept. Obstet. Gynecol., U. Washington, Seattle). *J Reprod Med* 12(5):194-196, 1974.

Previous studies have suggested that suppression of homograft rejection by azathioprine therapy is associated with increased risk of developing cervical carcinoma as well as reticulum cell sarcoma. Therefore, 35 women who had received kidney transplants at the University of Washington Hospitals were examined by cervical cytology and colposcopy from two wk to six yr after exposure to azathioprine. Minor abnormalities were found in nine women but one additional patient has developed a prolapsed submucous leiomyoma. It is recommended that women undergoing immunosuppressive therapy have Pap smears and colposcopic examinations twice yearly until the magnitude of the increased risk of neoplasia is known.

- 1505 IMMUNOTHERAPEUTIC AND IMMUNOPROPHYLACTIC EFFECTS OF BCG ON 3-METHYLCHOLANTHRENE-INDUCED AUTOCHTHONOUS TUMORS IN SWISS MICE. (E.) Tokunaga, T. (Natl. Inst. Hlth., Tokyo, Japan), S. Yamamoto, R. M. Nakamura and T. Kataoka. *J Natl Cancer Inst* 53(2):459-463, 1974.

The immunoprophylactic effects of bacillus Calmette-Guerin (BCG) on the development of tumors by 3-methylcholanthrene (MCA) in Swiss mice were investigated. During the 35-wk observation period after

the injection of MCA more than 80% of the control mice developed tumors. Intradermal injection with BCG (5×10^7) two wk prior to MCA administration (0.5 mg s.c.) significantly decreased tumor incidence; administration of BCG at the time mice were beginning to produce palpable tumors was ineffective. BCG was also injected directly into the tumors when a tumor grew more than 5 mm in diameter. Although control tumors without BCG developed progressively and killed the hosts, intratumor injection with BCG showed therapeutic effects on about 50% of the tumors. The fate of tumors after BCG injection varied, they showed either regression and cure, regression and relapse, retardation, or progression. Results of experiments with intratumor injection with BCG on K3 and K5 syngeneic tumors suggest growth rate and/or antigenicity of individual tumors are important in influencing the therapeutic effects of BCG.

1506 THE MOUSE MUTANT *NUDE* DOES NOT DEVELOP SPONTANEOUS TUMOURS. AN ARGUMENT AGAINST IMMUNOLOGICAL SURVEILLANCE. (E.) Rygaard, J. (Path. Anat. Inst., Kommunehospitalet, Copenhagen, Denmark) and C. O. Povlsen. *Acta Pathol Microbiol Scand (B)* 82(1):99-106, 1974.

The mouse mutant *nude* is immunologically deficient due to the congenital absence of the thymus. It will accept allografts and heterografts from closely and remotely related donors, its humoral response to a number of other antigens is also imperfect, and *de novo* malignancies can be induced by chemical carcinogens. The development of spontaneous tumors was studied in 11,000 *nude* mice from birth to 3-7 months of age (the normal life expectancy). Between 1969 and 1972, a total of 40,000 hours were spent observing these animals. No malignant changes were observed in any animal, and only one benign growth, a skin papilloma, was found. These results suggest that immune surveillance, if it exists, is a biological function of multicellular organisms which is specific in nature and different from cell-mediated and humoral immunity. Surveillance deficiencies may coincide with deficiencies in cell-mediated and/or humoral immunity, but only in a minority of these cases, indicating that surveillance may be a more primitive function.

1507 HEPATITIS B ANTIGEN: ANTIGENIC SITES RELATED TO HUMAN SERUM PROTEINS REVEALED BY AFFINITY CHROMATOGRAPHY. (E.) Neurath, A. R. (New York Blood Ctr., N.Y.), A. M. Prince and A. Lippin. *Proc Natl Acad Sci USA* 71(7):2663-2667, 1974.

Hepatitis B antigen-associated particles, isolated from sera of antigen carriers, were submitted to affinity chromatography on columns of insolubilized antibodies to normal human plasma. The particles adsorbed to the immunosorbent at pH 7.2 and were subsequently eluted at pH 2.2. Exposure of the particles to 8 M urea, 5 M KI, pH 2.2, detergents, organic solvents, or proteolytic enzymes failed to prevent their subsequent absorption to the immunosorbent. This suggests that antigenic determinants

related to human plasma proteins are constituent components of hepatitis B antigen-associated particles. These determinants are distinct from the group-specific and subtype-specific sites of the hepatitis B antigen and appear to be related to antigenic specificities on prealbumin, albumin, apolipoproteins C and D, and the γ -chain of immunoglobulin G.

1508 CYTOGENETIC STUDIES ON THE MECHANISM OF FORMATION OF ISOANTIGENIC VARIANTS IN SOMATIC CELL HYBRIDS. I. BANDING ANALYSES OF ISOANTIGENIC VARIANT SUBLINES DERIVED FROM THE FUSION OF TA3Ha CARCINOMA WITH MSWBS SARCOMA CELLS. (E.) Wiener, F. (Dept. Tumor Biol., Karolinska Inst., Stockholm, Sweden), T. Dalianis, G. Klein and H. Harris. *J Natl Cancer Inst* 52(6):1779-1796, 1974.

The MSWBS sarcoma, an isoantigenic loss variant selected from a near-diploid heterozygous tumor induced in an (A X ASW)_{F1} male mouse by 3-methylcholanthrene, lost one of the parental H-2 antigens by a mechanism that did not involve the loss of a whole chromosome bearing the relevant genetic determinant. But when the same selective procedures were used to select isoantigenic loss variants from hybrid cell tumors, loss of one parental H-2 antigen was associated with elimination of both chromosomes bearing that genetic determinant. This was established in an especially favorable hybrid line, Ta3Ha/MSWBS, in which both the #17 chromosomes bearing the H-2 determinants derived from TA3Ha were morphologically normal, and both the #17 chromosomes derived from MSWBS were involved in identifiable translocations.

1509 CARCINOEMBRYONIC ANTIGEN IN CANCER OF THE FEMALE REPRODUCTIVE SYSTEM: SEQUENTIAL LEVELS AND EFFECTS OF TREATMENT. (E.) Khoo, S. K. (Clin. Res. Unit, Walter Eliza Hall Inst. Med. Res., Melbourne, Australia) and E. V. Mackay. *Aust NZ J Obstet Gynaecol* 13(1):1-7, 1973.

The rate of disappearance of carcinoembryonic antigen (CEA) from the serum following treatment by surgery or irradiation was studied in 12 patients with carcinoma of the cervix, seven with carcinoma of the corpus uteri, eight with carcinoma of the ovary, five with carcinoma of the colon or rectum, and one each with carcinoma of the lung and bile duct. Following surgical excision, elevated levels of CEA fell within 2 wk if excision was complete, but remained elevated if excision was incomplete. In the cervical carcinoma patients, there was no decline in the levels of CEA within 10 wk of radical radiotherapy, indicating a continued release of CEA from tumor tissues undergoing radiation-induced necrosis. Persistently elevated levels of CEA were found in four patients with disseminated and inoperable cancers. Sequential levels of CEA in the serum appear to represent a good index of the effectiveness of surgical excision and should be of great value in postoperative followup.

- 1510 MACROPHAGE CONTENT OF TUMOURS IN RELATION TO METASTATIC SPREAD AND HOST IMMUNE REACTION. (E.) Eccles, S. A. (Chester Beatty Res. Inst., Sutton, Surrey, England) and P. Alexander. *Nature* 250(5468):667-669, 1974.

The macrophage content of tumors grown in immunosuppressed Hooded rats was monitored, as was the macrophage content of a Hooded rat sarcoma which was transplanted into August rats. When the rat fibrosarcoma was inoculated into the immunosuppressed rats, the incidence of spontaneous metastases was greatly increased. It is not possible to deduce from these experiments whether the simultaneous decrease in macrophage infiltration was causally related to the subsequent increase in metastases. A role for tumor macrophages in the control of tumor dissemination is suggested, however, by the parallel between macrophage content and the rate of spontaneous metastasis of a series of six different rat sarcomas grown in normal syngeneic recipients. The tendency to metastasize is also related (inversely) to the immunogenicity of the tumors, i.e., to the degree of resistance to tumor challenge in a suitable pre-immunized syngeneic recipient.

- 1511 IMMUNOLOGICAL DEMONSTRATION OF α -FETOPROTEIN IN UTERINE CYTOSOL FROM IMMATURE RATS. (E.) Aussel, C. (Inst. Sci. Res. Cancer, Villejuif, France), J. Uriel, G. Michel and E.-E. Baulieu. *Biochimie* 56(4):567-570, 1974.

The identity between serum α -fetoprotein and the estrogen-binding 4-5 S macromolecular complex of uterine cytosol from immature female Wistar rats (six, eight, ten, and 21 days) was demonstrated by the use of an immunoabsorbent specific to α -fetoprotein. Analysis of the sedimentation profile in glycerol gradients of uterine cytosol incubated with ^3H -estrone or ^3H -estradiol suggests that the total estrogen binding capacity of the 4-5 S complex is provided by α -fetoprotein. Decreases of α -fetoprotein content in rat uterus with the age of the animals indicate that this protein is probably present in the cytosol as a serum contaminant rather than as an intracytoplasmic constituent.

- 1512 THE DECLINE OF CELL-MEDIATED IMMUNITY IN AGING MICE. (E.) Menon, M. (Div. Biol. Med. Res., Argonne Natl. Lab., Ill.), B. N. Jaroslow and R. Koesterer. *J Gerontol* 29(5):499-505, 1974.

The influence of aging on cell-mediated immunity was studied in mice by two tests of allograft immunity. The results of *in vitro* ^{51}Cr release assay in C57Bl/6 mice showed a decline in cellular immunity by 85% in 16 months. From studies of the kinetics of cytotoxicity it was concluded that the spleens of older sensitized animals have fewer immunocytes without a loss of potency per cell. The primary response to skin allografts showed that older (two yr) B6CF₁ mice had slower rejection rates for allografts than younger animals (five-six months), while presensitized animals both young and old had equal rejection rates. The slower rejection rate in older mice is in accord

with the explanation that they produce fewer immunocytes. The age associated loss in cell-mediated immunity may contribute to increased carcinogenesis; but it may be beneficial to old transplant recipients who might thereby require less immunosuppressive therapy with its toxic side effects.

- 1513 STEROID-INDUCED MEDIASTINAL LIPOMATOSIS FOLLOWING KIDNEY TRANSPLANTATION. (Ger.) Wolf, A. (Med. U., Vienna, Austria), E. Lobenwein-Weinegg, W. F. Pinggera, F. Singer and H. K. Stummvoll. *Wein Z Inn Med* 54(5/6):248-253, 1973.

- 1514 LYMPHOCYTE DEPRESSIVE FACTOR PRODUCED BY A GUT CANCER. (E.) Edwards, A. J. (Hackney Hosp., London, England). *Ann R Coll Surg Engl* 54(6):270, 1974.

- 1515 A CONTRIBUTION TO BIOLOGY OF GRAWITZ'S KIDNEY TUMOR: HETEROTRANSPLANTATION. (E.) Uhlir, K. (Fac. Hosp., J. E. Purkyne U., Brno, Czechoslovakia), F. Rovny, M. Strmiska, E. Cerny and A. Navratilova. *Invest Urol* 12(1):23-26, 1974.

- 1516 LOCALIZATION WITHIN CLONED RAT PITUITARY TUMOR CELLS OF MATERIAL THAT BINDS ANTI-GROWTH HORMONE ANTIBODY. (E.) Masur, S. K. (Mt. Sinai Sch. Med., New York, N.Y.), E. Holtzman and F. C. Bancroft. *J Histochem Cytochem* 22(6):385-394, 1974.

- 1517 USE OF SPERM IN STUDYING CELL SURFACE DIFFERENTIATION. (E.) Hadden, J. W. (Sloan Kettering Inst., New York, N.Y.). *Clin Bull* 4(1):25-26, 1974.

- 1518 THE EFFECT OF SERUM PROTEIN CONCENTRATIONS ON THE SPECIFICITY OF THE RADIOIMMUNOASSAY OF CARCINOEMBRYONIC ANTIGEN IN MALIGNANT NEOPLASIA AND NON-NEOPLASTIC DISEASE. (E.) Crawley, J. M. (United Birmingham Hosp., England), B. E. Northam, J. P. G. King, J. C. Leonard, S. N. Booth and P. W. Dykes. *J Clin Pathol* 27(2):130-134, 1974.

- 1519 ORGANIZATION OF GLYCOLIPIDS AND GLYCOPROTEINS IN SURFACE MEMBRANES: DEPENDENCY ON CELL CYCLE AND ON TRANSFORMATION. (E.) Gahmberg, C. G. (Sch. Pub. Hlth., U. Washington, Seattle) and S.-I. Hakomori. *Biochem Biophys Res Commun* 59(1):283-291, 1974.

- 1520 A NEW CASE OF IgD-MYELOMA ASSOCIATED WITH HYPOGAMMAGLOBULINEMIA. (E.) Oppenheim, W. (Civil Hosp., Udine, Italy). *Beitr Pathol* 151(1):97-102, 1974.

- 1521 IMMUNODIFFUSION ANALYSIS OF THE ANTIGENS OF MOUS LEUKEMIAS. (Rus.) Lezhneva, O. M. (USSR Acad. Med. Sci., Moscow). *Biull Eksp Biol Med* 77(5):82-85, 1974.

(1522-1537)

1522 BIOSYNTHESIS OF GLOBOSIDE AND FORSSMAN-RELATED GLYCOSPHINGOLIPID IN MOUSE ADRENAL Y-1 TUMOR CELLS. (E.) Yeung, K.-K. (Dept. Chem., U. Notre Dame, Ind.), J. R. Mosdal, J.-L. Chien, D. A. Gardner and S. Basu. *Biochem Biophys Res Commun* 59(1):252-260, 1974.

1523 THYOMA WITH SYSTEMIC LUPUS ERYTHEMATOSUS, RED BLOOD CELL APLASIA, AND HERPESVIRUS INFECTION. (E.) Takigawa, M. (Fac. Med., Kyoto U., Japan) and M. Hayakawa. *Arch Dermatol* 110(1):99-102, 1974.

1524 IMMUNOFLUORESCENT LOCALIZATION OF IMMUNOGLOBULINS IN NASAL POLYPS. (E.) Bass, R. M. (Northwest. U., McGaw Med. Ctr., Chicago, Ill.), E. V. Potter and P. L. Barney. *Arch Otolaryngol* 99(6):446-448, 1974.

1525 MYELOMA PRODUCING NONSECRETORY IgM AND SECRETORY IgG. (E.) Stein, H. (Inst. Pathol., U. Kiel, Germany) and E. Kaiserling. *Scand J Haematol* 12(4):274-283, 1974.

1526 HOST-RELATED FACTORS DETERMINE THE OUTGROWTH OF TERATOCARCINOMAS FROM MOUSE EGG-CYLINDERS. (E.) Damjanov, I. (Med. Fac., U. Zagreb, Yugoslavia) and D. Solter. *Z Krebsforsch* 81(1):63-69, 1974.

1527 HUMAN BREAST CANCER AND THE AUTOCHTHONOUS LYMPH NODE CELL RESPONSES: A TISSUE CULTURE AND ULTRASTRUCTURAL STUDY. (E.) Richters, A. (Dept. Pathol., U. South. California, Los Angeles) and R. P. Sherwin. *Cancer* 34(2):328-337, 1974.

1528 THE DELAYED HYPERSENSITIVITY REACTION IN BREAST CANCER. (E.) Roberts, M. M. (Welsh Natl. Sch. Med., Cardiff) and W. Jones-Williams. *Br J Surg* 61(7):549-552, 1974.

1529 INCREASED PRODUCTION OF α -FETOPROTEIN BY CYCLIC 3',5'-ADENOSINE MONOPHOSPHATE-TREATED YOSHIDA ASCITES SARCOMA CELLS *IN VITRO*. (E.) Isaka, H. (Sch. Med., Yokohama City U., Japan), S. Umehara, M. Umeda, H. Hirai, Y. Tsukada and H. Watabe. *GANN* 65(1):79-83, 1974.

1530 TONSILLECTOMY AND HODGKIN'S DISEASE. (E.) Vianna, N. J. (Cancer Control Bur., New York State Hlth. Dept., Albany), P. Greenwald, A. Polan, M. D. Keogh and J. N. P. Davies. *Lancet* (7873):168-169, 1974.

1531 DEMONSTRATION OF ALPHA-FETOGLOBULIN IN HEPATOMA TISSUE BY FLUORESCENT ANTIBODY TECHNIQUE. (E.) Chu, M. L. (Coll. Med., Natl. Taiwan U., Taipei), W.-S.-J. Lin, T. O. Yoshida, S.-H. Chu and T.-Y. Lin. *Cancer* 34(2):268-273, 1974.

1532 INFLUENCE OF SIMULTANEOUS PINEALECTOMY AND THYMECTOMY ON THE GROWTH AND FORMATION OF METASTASES OF THE YOSHIDA SARCOMA IN RATS. (E.) Lapin, V. (Cancer Res. Inst., U. Vienna, Austria). *Exp Pathol* 9(1/2):108-112, 1974.

1533 IMMUNOGLOBULIN SYNTHESIS BY FREE POLYSOMES OF MOUSE MYELOMA CELLS. (E.) Baglioni, C. (Dept. Biol. Sci., State U. New York, Albany) and P. Liberti. *Mol Biol Rep* 1(6):329-335, 1974.

1534 DEPLETION OF THYMUS DEPENDENT LYMPHOCYTES IN HODGKIN'S DISEASE. (E.) Anderson, E. (Gentofte Hosp., Copenhagen, Denmark). *Scand J Haematol* 12(4):263-269, 1974.

1535 PLASMACYTOMA WITH COEXISTENCE OF TWO DIFFERENT CLASSES OF IMMUNOGLOBULINS (IgG and IgA). (Pol.) Bobnis, W. (Med. Acad., Szczecin, Poland) and M. Moyke. *Wiad Lek* 27(3):265-268, 1974.

1536 BLOOD GROUP SUBSTANCE A IN CARCINOMAS OF THE LARYNX. (E.) Dabelsteen, E. (Roy. Dental Coll., Copenhagen, Denmark), N. Mygind and B. Henriksen. *Acta Otolaryngol* 77(5):360-367, 1974.

1537 CELL SURFACE IMMUNOGLOBULIN. VI. DYNAMICS ON A HUMAN LYMPHOMA LINE. (E.) Grundke-Iqbal, I. (Irvington House Inst., New York, N.Y.) and J. W. Uhr. *Eur J Immunol* 4(3):159-163, 1974.

See also:

- * (Rev): 1209, 1210, 1211, 1212, 1213, 1214
- * (Chem): 1272
- * (Viral): 1362, 1363, 1371, 1373, 1375, 1377, 1382, 1385, 1390, 1411
- * (Epid-Biom): 1569, 1606

- 1538 BIOCHEMICAL PROPERTIES OF NEOPLASTIC CELL MITOCHONDRIA. (E.) White, M. T. (Cancer Res. Lab., U. California, Berkeley), D. V. Arya and K. K. Tewari. *J Natl Cancer Inst* 53(2):553-559, 1974.

Mitochondria from monolayer cultures of Novikoff hepatoma cells were studied for their biochemical and structural organization and compared with mitochondria from solid Novikoff hepatoma and normal liver. Cultured cell and tumor mitochondria were similar in both ultrastructure and biochemical properties. Both differed distinctly from liver mitochondria, in that they had drastically reduced activities of several flavoprotein enzymes associated with their outer and inner membranes and altered morphology of their matrix as evident from electron micrographs. The alterations observed in the Novikoff hepatoma mitochondria were not the result of varied growth conditions but were inherent in these neoplastic cells. Mitochondria from another neoplastic cell line, hamster melanoma CCL 49, grown *in vitro* were compared with mitochondria from cultures of a non-neoplastic cell line hamster embryo Nil 2. Melanoma cell mitochondria showed reductions in outer and inner membrane flavoproteins similar to those observed in Novikoff hepatoma mitochondria. There were significant reductions in the activities of NADH oxidase, NADH-cytochrome c reductase, and adenylate kinase. In addition, monoamine oxidase was absent.

- 1539 THE INHIBITION OF ARGINASE BY PROLINE IN CELL-FREE EXTRACTS OF MOUSE MAMMARY TUMOUR. (E.) Rao, K. V. (Cancer Res. Inst., Tata Memorial Ctr., Parel, Bombay, India), S. R. Pai and C. V. Bapat. *Br J Cancer* 30(2):129-136, 1974.

The effects of glutamic acid and proline on arginase activity in mouse mammary tumors were investigated. Arginase activity was found to be increased in precancerous nodules and mammary tumor when compared with the mammary gland. Proline inhibited the mammary tumor arginase and up to 30 mM concentration the inhibition followed first order kinetics. Hill analysis of the inhibition of arginase by proline showed that proline inhibited the arginase activity by competing directly at the active site without conformational change. The inhibition may be of regulatory importance, involving a feedback mechanism in mammary tumors.

- 1540 INTERACTIONS OF SEPARATE TYPES OF CELLS DURING NORMAL AND NEOPLASTIC MAMMARY GLAND GROWTH. (E.) Slemmer, G. (Cancer Res. Ctr., U. British Columbia, Vancouver, Canada). *J Invest Dermatol* 63(1):27-47, 1974.

Using transplantation methods and histocompatibility markers, the cellular composition of normal and neoplastic tissues derived from mouse mammary glands composed to cells of two different genotypes were studied. The normal mammary glands consisted of three different cell types: alveolar epithelial, ductal epithelial, and myoepithelial. Different etiologic factors caused the neoplastic transforma-

tion of the different cell types. Each type produced a characteristic morphologic class of premalignant lesions which progressed to characteristic malignancies. Alveolar epithelial cells produced alveolar and acinar glandular neoplasia, while ductal epithelial neoplasms had a ductal-papillary morphology. Myoepithelial neoplasias were usually characterized by epidermoid-mesenchymoid metaplasia. Some neoplastic premalignant epithelial cells were associated with normal myoepithelial cells, while the malignant variants were not. Some myoepithelial neoplasms contained normal parenchymal cells components, but the neoplastic cells did not require this association. Existing classification systems do not separate mammary neoplasms on the basis of the cell type of origin. This can be done, however, by analyzing variants from premalignant precursors of known cellular composition.

- 1541 DIFFERENTIATION *IN VITRO* OF NORMAL MOUSE EMBRYOS AND MOUSE EMBRYONAL CARCINOMA. (E.) Hsu, Y.-C. (Dept. Pathobiol., Johns Hopkins U., Baltimore, Md.) and J. Baskar. *J Natl Cancer Inst* 53(1):177-185, 1974.

The authors present results of studies to determine whether embryoid bodies derived from mouse teratocarcinoma can differentiate *in vitro* in the same medium as do normal mouse embryos of a corresponding stage. Mouse blastocysts of 3.5 days' gestation and embryoid bodies derived from the transplantable teratocarcinoma OTT6050 of strain 129/Sv-S1^J CP mice were cultured in Eagle's minimum essential medium (MEM) supplemented with 10% calf serum. The normal mouse embryos differentiated *in vitro* to the early somite stage, with blood circulation and heartbeat equivalent to those of normal 9-day mouse embryos. The embryoid bodies also differentiated *in vitro*. The disorganized embryonal carcinoma in the core of the embryoid body became well-organized and formed rosettes, with the long axis of the cells perpendicular to the center of the cavity. The embryoid bodies, which proliferated by budding, formed up to 30 polycysts, each with an inner core of relatively well-organized ectoderm surrounded by 1 cell layer of endoderm. Mesoderm later differentiated between the endoderm and ectoderm. Some embryoid bodies developed yolk sacs with blood islands containing primary red blood cells. Other embryoid bodies developed nodules of squamous cell epithelium enclosing a keratin substance in the core. Neither squamous cell epithelium nor keratin substances was observed in the normal embryos which differentiated *in vitro*.

- 1542 INFLUENCE OF SEEDING DENSITY ON MULTICELLULAR ORGANIZATION AND NUCLEAR EVENTS IN CULTURES OF NORMAL AND NEOPLASTIC MOUSE MAMMARY EPITHELIUM. (E.) Das, N. K. (Cancer Res. Lab., U. California, Berkeley), H. L. Hosick and S. Nandi. *J Natl Cancer Inst* 52(3):849-861, 1974.

Normal mammary tissue, mammary tumors, and 16-day embryos of BALB/c strain mice were dissociated into single cells which were plated at high (5×10^5 cells/cm²), medium (1×10^5 cells/cm²), and low densities

$\times 10^4$ cells/cm²) in a defined culture medium supplemented with fetal calf serum, insulin, and hydrocortisone. Cell shape, total DNA, DNA synthesis, and incidence of mitoses were determined and compared in the various cultures over a period of a few weeks. In the transplanted tumors used, more than 60% of the nuclei were initially 4C; these rapidly reached high ploidies in low density culture. Nuclei of normal cells were uniformly 2C and became polyploid only after several days in culture at low density. Cultures of normal and tumor-derived epithelial cells were similar in other respects at all three densities. Embryo fibroblasts cultured under the same conditions grew to high densities of predominantly polyploid cells at all the plating densities used. In the primary cultures studied, tumor cell properties were very similar to those of the homologous normal cells. If, as is believed, these properties in primary culture closely approximate properties *in vivo*, then the difference between normal and neoplastic primary growth must be very subtle.

143 THE BRENNER TUMOR AND THE WALTHARD CELL NEST: AN ELECTRON MICROSCOPIC STUDY. (E.) Sch, L. M. (Indiana U. Sch. Med., Indianapolis). *Invest* 31(1):15-23, 1974.

The relationship of Brenner tumor to the Walthard cell nest was studied by electron microscopy. Ovarian Brenner tumors are composed of a urothelial type epithelium and a stroma similar to the ovarian stroma. Cortically situated Brenner tumors appear to originate from the celomic epithelium by a process of metaplasia, whereas more centrally located tumors may be derived from hilar structures. A Brenner tumor from a 51-yr-old Negro woman and Walthard cell nests from a 45-yr-old Negro woman were studied by light and electron microscopy. These indicated similarities in structure between the Brenner tumor, the Walthard cell nests, and normal urinary bladder epithelium. The Walthard cell nests exhibited an ultrastructure which was similar to, but less complex than, that of the Brenner tumor. The fine structure of the Brenner tumor differed significantly from those of mesotheliomas and adenomatous tumors. The cells of the Brenner tumor can also be distinguished from those of serous tumors of the ovary, clear cell carcinomas of the female genital tract, and granulosa cell tumors. The stroma of the Brenner tumor resembled inactive ovarian stroma.

144 MEGAKARYOCYTE POLYPLOIDIZATION IN ACUTE LEUKAEMIA AND PRELEUKAEMIA. (E.) Queisser, (Fac. Med., Mannheim U., Heidelberg, W. Germany), Queisser, M. Ansmann, G. Brunner, D. Hoelzer and Heimpel. *Br J Haematol* 28(2):261-270, 1974.

Megakaryocyte polyploidy was studied in six cases of preleukemic acute leukemia (PL), five cases of overt acute leukemia (AL), and three cases of acute leukemia in complete remission. The megakaryocyte polyploidization was determined cytophotometrically, in some cases, by *in vitro* labeling with tritiated thymidine (³H-TdR). In both PL and overt AL, there was an impairment of the ³H-TdR labeling index

and altered megakaryocyte polyploidy as indicated by a decrease in the maximum polyploidization capacity (five cases), evidence of diploid megakaryocytes (two cases), and evidence of hyperploid megakaryocytes (six cases). These disturbances reflected the cytological abnormalities (microkaryocytes, polykaryocytes) observed in most of the cases studied. In contrast, in the AL cases in remission, a normal labeling index and polyploidy composition were observed, suggesting that the polyploidization disturbances are reversible. A strict correlation between the polyploidization defect and the platelet production could not be established from the cases studied.

1545 VAGINAL ADENOSIS: A PRECANCEROUS LESION? (E.) Staffl, A. (Med. Coll. Wisconsin, Milwaukee) and R. F. Mattingly. *Am J Obstet Gynecol* 120(5):666-677, 1974.

The prenatal administration of diethylstilbestrol (DES) during the period of vaginal organogenesis alters the embryologic localization of the original squamocolumnar junction which may be established anywhere in the vagina rather than on the cervix. Exposure of the columnar epithelium to the vaginal environment and to the low pH of the vagina stimulates the development of squamous metaplasia. Colposcopically, this squamous metaplasia is part of a large transformation zone which, in some cases, involves the entire vagina. The major clinical significance of this entity relates to the fact that in DES-exposed girls, abnormal colposcopic findings (white epithelium, mosaic pattern, punctation) are present within the transformation zone in 97% of cases, as compared with only 8% in unexposed girls. This highly significant difference suggests that the major clinical risk in DES-exposed girls is the potential development of squamous neoplasia rather than the rarely associated clear-cell adenocarcinoma. In a colposcopic and histologic study of 131 cases of vaginal adenositis in DES-exposed girls, two cases of squamous carcinoma *in situ*, two cases of severe dysplasia, and three cases of moderate dysplasia were diagnosed.

1546 PRIMARY LIVER CARCINOMA. (E.) Linder, G. T. (Louisiana State U. Sch. Med., New Orleans), J. N. Crook and I. Cohn, Jr. *Cancer* 33(6):1624-1629, 1974.

From 1948 through 1970, 164 histologically diagnosed cases of primary liver carcinoma were managed at Charity Hospital in New Orleans. The disease was five times more common in males, and most frequently occurred in the sixth and seventh decades of life. Weight loss, upper abdominal pain, anorexia, and jaundice made up the most significant symptom complex. Hepatomegaly was the most common physical finding. Approximately 85% of the cases were hepatocellular carcinoma. Extra-hepatic metastases were present in 55% of the 120 cases which came to autopsy. Lung, regional nodes, adrenals, and bone were the favored sites. Tumor was limited to one lobe in 32% of cases. Cirrhosis of the liver was diagnosed

in 56%. Six patients underwent hepatic resection; one lived for more than three yr and one is alive 3½ yr after operation. Twelve patients received chemotherapy; one was alive at 2½ yr. Forty-nine patients had an intra-abdominal operative procedure. Overall survival data for operated vs non-operated cases did not vary significantly. Twenty-seven patients had percutaneous liver biopsy; the death of three was directly attributable to intra-abdominal hemorrhage after this procedure.

- 1547 HISTOPATHOLOGICAL ANALYSIS OF BENIGN POLYPS IN PATIENTS WITH CARCINOMA OF THE COLON AND RECTUM. (E.) Ekelund, G. (Malmo Gen. Hosp., Sweden) and C. Lindstrom. *Gut* 15(8):654-663, 1974.

Between 1958 and 1967, 960 patients with colorectal cancer were admitted to the only surgical department in Malmo, Sweden. Polyps were found in 22% of these patients (median age 65-69), a total of 471 polyps being found among 215 patients. Of these polyps, 381 were examined histologically. Eighty-one percent of the polyps were benign epithelial neoplasms, 12% were metaplastic, and 7% were of miscellaneous types. Almost 1/4 of the benign epithelial neoplasms were adenovillous lesions, 63% of them being found in men. The benign epithelial neoplasms tended to be situated in the vicinity of the coexisting carcinoma. The differentiation of benign epithelial neoplasms tended to be poorer with decreasing distance from the anus and increasing size of the lesion; the differentiation was usually poorer in men than in women. None of the metaplastic polyps were found in patients aged less than 50 yr, 84% being found in the sigmoid colon or rectum. The metaplastic polyps were generally associated with other types of benign polyp. The metaplastic polyps rarely exceeded 5 cm in diameter. The findings support the assumed relationship between benign epithelial neoplasms and adenocarcinoma of the colon and rectum.

- 1548 TUMOURS OF THE LYMPHORETICULAR SYSTEM: NOMENCLATURE, HISTOGENESIS, AND BEHAVIOUR. (E.) Gowing, N. F. C. (Roy. Marsden Hosp., London, England). *J Clin Pathol* 27(7):103-107, 1974.

- 1549 NEUROMA FORMATION IN THE CEREBELLO-PONTINE ANGLE FOLLOWING TRAUMATIC AVULSION OF THE TRIGEMINAL ROOT. A CLINICO-MORPHOLOGICAL CONTRIBUTION. (Ger.) Holdorff, B. (Steglitz Clin., Free U., Berlin, Germany), J. Cervos-Navarro and E. Fuchs. *Acta Neurochir* 29(3/4):247-256, 1973.

- 1550 BRENNER TUMORS AND WALTHARD CELL NESTS. (E.) Bransilver, B. R. (Coll. Phys., Surg. Columbia U., New York, N.Y.), A. Ferenczy and R. M. Richart. *Arch Pathol* 98:76-86, 1974.

- 1551 ORIGIN OF HODGKIN'S CELL. (E.) Kadin, M. E. (U. California, Sch. Med., San Francisco), S. R. Newcom, S. B. Gold and D. P. Stites. *Lancet* (7873):167-168, 1974.

- 1552 STUDIES OF INTESTINAL METAPLASIA IN THE GASTRIC MUCOSA BY DETECTION OF DISACCHARIDASES WITH "TES-TAPE". (E.) Kawachi, T. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan), K. Kogure, N. Tanaka, A. Tokunaga, T. Sugimura, Y. Koyama, K. Kanasugi, T. Hirota and R. Sano. *J Natl Cancer Inst* 53(1):19-30, 1974.

- 1553 FORMATION OF PIGMENT OF LIPID NATURE IN ANIMAL TISSUES DURING NEOPLASTIC DEVELOPMENT AND IRRADIATION. (Rus.) Vertushkov, V. T. (Biol. Fac., M. V. Lomonosov Moscow State U., USSR), I. I. Ivanov and B. N. Tarusov. *Biofizika* 19(2):295-299, 1974.

- 1554 PERITONEAL GLIOMATOSIS PRODUCED BY OVARIAN TERATOMAS. (E.) Nogales, Jr., F. F. (Gynecol. Dept., U. Complutense, Madrid, Spain) and H. A. Oliva. *Obstet Gynecol* 43(6):915-920, 1974.

- 1555 CYTOLOGIC STUDIES IN CASES WITH CARCINOMA *IN SITU* AND MICROINVASIVE CARCINOMA OF THE UTERINE CERVIX. (E.) Rubio, C. A. (Karolinska Inst., Stockholm, Sweden). *Acta Pathol Microbiol Scand (A)* 82(1):161-168, 1974.

- 1556 THE FINE STRUCTURE OF A POSSIBLE CARCINOMA-*IN-SITU* IN THE SEMINIFEROUS TUBULES IN THE TESTIS OF FOUR INFERTILE MEN. (E.) Nielsen, H. (U. Inst. Pathol. Anat., Copenhagen, Denmark), M. Nielsen and N. E. Skakkebaek. *Acta Pathol Microbiol Scand (A)* 82(2):235-248, 1974.

- 1557 CYTOPHOTOMETRIC STUDY OF PAPILLARY OVARIAN CYSTOMAS. BORDERLINE CASES OF MALIGNANCY. (Ger.) Sachs, H. (U. Clin. Obstet. Gynecol., Hamburg-Eppendorf, Germany), H.-E. Stegner and K. Wurthner. *Beitr Pathol* 151(1):42-64, 1974.

- 1558 MALIGNANT TRANSFORMATION IN OVARIAN ENDOMETRIOSIS. (E.) Hejda, V. (Inst. Care Mother Child, Prague, Czechoslovakia) and J. Bohacova. *Neoplasma* 21(1):69-74, 1974.

- 1559 CONVERSION OF HODGKIN'S DISEASE TO LYMPHOBLASTIC LYMPHOSARCOMA. (E.) Mims, C. H. (U. Texas Med. Branch, Galveston) and J. J. Costanzi. *Oncology* 29(3):238-243, 1974.

- 1560 MELANOTIC NERVE SHEATH TUMORS. (E.) Mandybur, T. I. (Cincinnati Gen. Hosp., Ohio). *J Neurosurg* 41(2):187-192, 1974.

- 1561 THE POLYP-CANCER SEQUENCE IN THE LARGE BOWEL. (E.) Morson, B. (St. Mark's Hosp., London, England). *Proc R Soc Med* 67(6):451-457, 1974.

1562 INVERTED PAPILLOMA OF THE BLADDER. (E.)
 Cummings, R. (Dept. Pathol., U. Tasmania,
Australia). *J Pathol* 112(4):225-227, 1974.

See also:

- * (Rev): 1203, 1215, 1219, 1221, 1224, 1227, 1228
- * (Chem): 1285, 1288, 1306
- * (Phys): 1353
- * (Viral): 1382, 1438

- 1563 FAMILIAL OCCURRENCES OF A VARIETY OF PRE-MALIGNANT DISEASES AND UNCOMMON MALIGNANT NEOPLASMS. (E.) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.), A. J. Krusch, G. M. Mulcahy and W. B. Reed. *Cancer* 33(5):1474-1479, 1974.

The occurrence of a variety of premalignant diseases and uncommon malignant neoplasms was studied in a large segment of an inbred midwestern kindred of Dutch ancestry; the kindred contains more than 2000 genetic relatives. The proband of the branch studied died with bronchopneumonia and abscesses of the brain due to *Candida albicans*; Fanconi's aplastic anemia was considered as a possible diagnosis. His younger sister appeared to be affected with a variety of Fanconi's anemia with certain clinical features of Bloom's and other syndromes. Malignant testicular neoplasms were histologically verified in four relatives (two seminomas, one malignant teratoma, and one combined type tumor). The incidence of testicular cancer in this branch of the kindred is 286 cases per 100,000 per year, compared with a predicted 4.03 cases per 100,000 per year. Among 22 other generally rarely occurring cancers found among this branch of the kindred were two cases of Wilm's tumor, one case of thymic carcinoma, and one case of astrocytoma. Several hereditary precancerous diseases also occurred among the family members including xeroderma pigmentosum which was found in two siblings. At present there is no satisfactory etiologic explanation for the occurrence of these conditions in this family. Environmental factors common to the family cannot be excluded and hereditary factors conditioned strongly by consanguinity may be operating in concert with as yet unknown nongenetic factors such as an oncogenic virus.

- 1564 HIGH INCIDENCE OF SPONTANEOUS URINARY BLADDER AND URETER TUMORS IN THE BROWN NORWAY RAT. (E.) Boorman, G. A. (Inst. Exp. Gerontol. TNO, Rijswijk (ZH), Netherlands) and C. F. Hollander. *J Natl Cancer Inst* 52(3):1005-1008, 1974.

The occurrence of tumors of the bladder and ureter was studied in 369 Brown Norway (BN/BiRij) rats, 222 of which were allowed to complete their normal lifespan. Tumors of the bladder were more common in males (28% versus 2% in females) whereas the reverse was true of tumors of the ureter (20% in females, 6% in males). Most of the bladder tumors were papillary and covered by a thickened and moderately pleomorphic transitional epithelium. The tumors of the ureter were similar to those of the urinary bladder, except that they had a much greater tendency to form areas of squamous cells and keratinize. In both bladder and ureter, atypia of the adjacent epithelium was usual. Granulocytes, plasma cells, and lymphocytes were frequent in the wall of the ureter, the inflammatory component being less prominent in the bladder. Metastasis occurred in four rats with ureter tumors and one rat with a bladder tumor. WAG/Rij rats kept at the same time under identical conditions failed to develop bladder or ureter tumors. Preliminary data suggest a correlation between the occurrence of tumors and the urinary calculi frequently found in this strain. The Brown Norway rat may therefore be a useful animal model for the study of urinary bladder tumors.

- 1565 ESOPHAGEAL CANCER AND HOT TEA. (E.) Brunning, D. A. (Chester Beatty Res. Inst., London, England). *Lancet* I(7851):272, 1974.

The tea drinking habits of 301 esophageal cancer patients and 301 healthy controls from the Aktubinsk province of Kazakhstan were compared. Of the esophageal patients, 129 men (90.32%) and 158 women (99.34%) consumed more than six small glasses of excessively hot tea at one time, the corresponding figures for the controls being 79.58% of the men and 98.12% of the women. The difference between the two groups appeared to be too small to establish hot tea as the main factor responsible for the increased incidence of esophageal cancer among the Kazakhs. However, in an earlier study, it was found that the drinking of very hot tea was prevalent among 63 (49.6% Kazakhs with esophageal cancer, as compared with only 17 (23.6%) controls. The standardized morbidity rate per 100,000 inhabitants of the city of Guryev was 240.2 for Kazakhs and 93.4 for Russians. In addition to drinking very hot tea, the esophageal cancer patients tended to consume excessively hot food, overeat before retiring, eat hastily, and eat dry uncooked solids. These findings justify further investigation.

- 1566 CANCER OF THE CERVIX: A SEXUALLY TRANSMITTED INFECTION? (E.) Singer, A. (Jessop Hosp. Women, Sheffield, England). *Lancet* II(7871):41, 1974.

Although both multiple sexual partners and early age of first coitus are significant variables in the etiology of cervical cancer, it is the latter which predominates in most large epidemiological studies of cervical malignancy. Trends toward premarital coitus have been increasing in recent years, and the incidence of cervical premalignant and malignant disease has been increasing in women born just before this "era" of change. The recently reported increased rate of cervical malignancy in wives of husbands with prostatic cancer indicates that an infectious agent, most likely viral, is in some way involved in mutagenesis in both these sites. It is possible that retrograde involvement of the spermatogenic mechanism by this agent could endow some male gamete with a neoplastic potential. The stability of cohort trends implies that potentially high-risk groups of women exist who will require close surveillance throughout their lives. Early detection in these high-risk groups is of paramount importance.

- 1567 CHEMODECTOMAS IN DOGS: EPIDEMIOLOGIC COMPARISONS WITH MAN. (E.) Hayes, H. W., Jr. (Natl. Cancer Inst., Bethesda, Md.) and J. F. Fraumeni Jr. *J Natl Cancer Inst* 52(5):1455-1458, 1974.

Fifty dogs with microscopically confirmed primary chemodectomas were identified at 11 veterinary school clinic-hospitals throughout the United States and Canada. All of the chemodectomas were either aortic or carotid body tumors, the former being 4.8 times as common as the latter. Compared with the other purebred animals, the boxer and Boston terrier breeds

both brachycephalic) were at significantly higher risk. Males had a nonsignificantly higher risk than females. The risk for dogs 10 yr of age or older was 17 times that for younger animals. Of the tumors occurring simultaneously with the chemodectomas, the most common were seminoma, interstitial-cell tumor of the testis, thyroid gland neoplasm, and hemangioma. The observed number of cases of each of these groups of concomitant tumors significantly exceeded the number of cases expected. In man, the reported tendency of multiple primary tumors in conjunction with chemodectoma has been confined to the chemoreceptor system. The etiologic role of chronic hypoxia, suggested by the high incidence of carotid body tumors among Peruvians in the Andes, may be clarified by further studies of chemodectoma in the brachycephalic breeds.

568 HODGKIN'S DISEASE AMONG JAPANESE AMERICANS. (E.) Mason, T. J. (Nat'l. Cancer Inst., Bethesda, Md.) and J. H. Fraumeni, Jr. *Lancet* 2(7850): 15, 1974.

Mortality statistics for Hodgkin's disease in Western countries show peaks at 15-34 yr and 50+ yr; in Japan the disease is nearly absent in young adults. Compared with native Japanese, the mortality rates from Hodgkin's disease among Japanese Americans between 1950 and 1969 are significantly higher in the 15-34 and 50+ age groups. Despite limitations in these data, the shifts in mortality among U.S. Japanese toward the rates prevailing in the White population are consistent with an environmental influence at all ages, and do not support the notion that the young adult disease has distinctive characteristics of an infectious process.

569 CERVICAL CANCER IN YUGOSLAVIA. I. ANTIBODIES TO GENITAL HERPESVIRUS IN CASES AND CONTROLS. (E.) Kessler, I. I. (Johns Hopkins U., Sch. Hyg. Pub. Hlth., Baltimore, Md.), Z. Kulcar, M. E. Rawls, S. Smerdel, M. Strnad and A. M. Lilienfeld. *J Nat'l Cancer Inst* 52(2):369-376, 1974.

A broadly based epidemiologic investigation of cervical cancer, with special reference to the herpesvirus hypothesis, was recently completed in Yugoslavia. A total of 350 women less than 65 yr old with histologically confirmed squamous carcinoma of the uterine cervix and an equal number of other currently hospitalized women were interviewed, examined, and bled for measurement of neutralizing antibodies to oral (HSV-1) and genital (HSV-2) herpesviruses. No pattern was discernible in the distribution of HSV-1 titers. However, for both Moslems and non-Moslems in each age group studied, as well as in all combined, HSV-2 titers were higher among cases than controls. The ratio of HSV-2 to HSV-1 mean log titers was also significantly higher in each group of cases than in the corresponding controls. Furthermore, HSV-2 antibody prevalence as judged by II/I titer ratios greater than 84 was significantly greater among cases than among controls, both Moslem and non-Moslem, with a relative risk of approximately 2. The consistent direction of these findings lends further credence to the herpesvirus hypothesis in cervical cancer.

1570 HORIZONTAL TRANSMISSION OF LEUKAEMIA. (E.) Parker, J. E. (Lions Gate Hosp., North Vancouver, British Columbia, Canada). *Lancet* 2(7850): 210-211, 1974.

Between 1958 and 1973, 18 cases of acute leukemia occurred within the prepubertal age-group of the North Shore of Burrard Inlet in Vancouver, Canada. Eight of these children developed the disease within 1 year of changing domicile and six of them were in an older area of town within a 3/4-mile radius. Since there was no pairing by year of diagnosis within this group, the aggregation may have been fortuitous. However, three men in their 30s developed acute leukemia approximately 5 years after contact with a child who had leukemia or who later developed leukemia. The occurrence of acute leukemia in adult next-door neighbors in two further situations raises the possibility of horizontal transmission in the adult variety at least. In cats, leukemia may be due to a virus which is transmitted horizontally, and a similar situation may exist in man.

1571 BOWEL TRANSIT-TIMES IN TWO POPULATIONS EXPERIENCING SIMILAR COLON-CANCER RISKS. (E.) Glober, G. A. (Japan-Hawaii Cancer Study, Nat'l. Cancer Inst., Honolulu), J. O. Moore, K. L. Klein and B. C. Abba. *Lancet* (7872):80-81, 1974.

Japanese living in Hawaii have a higher incidence of colon cancer than Japanese living in Japan and approximately the same risk as American Caucasians living in Hawaii. Bowel transit times (BTT) were measured in 63 Hawaiian men of Japanese ancestry and 23 Caucasian men of the same age (50-74 yr). The BTT was faster among the Japanese than among Caucasians, and there was no significant difference between the first-generation (Issei) and second-generation (Nisei) Japanese. Age, education, and occupation did not significantly affect the BTT. The Japanese tended to defecate more frequently than the Caucasians. There were no significant correlations between body surface areas or weights and BTT. Thus, with regard to the Hawaiian-Japanese experience, BTTs do not seem to be related to the pathogenesis of colonic disease.

1572 HODGKIN'S DISEASE IN PATIENTS WITH PREVIOUS INFECTIOUS MONONUCLEOSIS: 30 YEARS' EXPERIENCE. (E.) Rosdahl, N. (Dept. Med. Microbiol., U. Copenhagen, Denmark), S. O. Larsen and J. Clemmesen. *Br Med J* 2(5913):253-256, 1973.

Between 1938 and 1970, 17,073 people in Denmark gave positive reactions (titer of 1/32 or higher) to the Paul-Bunnell test. Of these persons, 17 developed Hodgkin's disease at least 12 months later. Sixteen of these patients were men, which is significantly different from the expected sex ratio for Hodgkin's disease. The total number of patients with Hodgkin's disease also significantly exceeded the expected number. Twelve of the 17 patients had had verified infectious mononucleosis this being a significantly greater number than expected; the sex ratio among this group was also significantly different from that expected. These findings suggest that infectious mononucleosis and Hodgkin's disease may be associated.

- 1573 COMPARATIVE INCIDENCE OF BRONCHOGENIC CARCINOMA IN SUBJECTS WITH CENTRILOBULAR AND PANLOBULAR EMPHYSEMA. (E.) Anderson, A. E., Jr. (Baptist Mem. Hosp., Gainesville, Fla.) and A. G. Foraker. *Cancer* 33(4):1017-1020, 1974.

Twenty-one cases of centrilobular emphysema (19 men) and 19 cases of panlobular emphysema (11 men) were analyzed for the comparative incidence of bronchogenic carcinoma. The morphological characteristics of these cases had previously been studied. Seven of the centrilobular emphysema patients had bronchogenic carcinoma, while none of the panlobular emphysema patients had lung cancer in the opposite lung; this difference is significant. All cases of lung cancer in conjunction with centrilobular emphysema occurred in men, while none of the men with panlobular emphysema were so affected. The data suggest a much stronger tie between centrilobular emphysema and lung cancer than between panlobular emphysema and lung cancer. The frequent co-existence of the former two conditions may reflect separate effects of a common etiologic agent, i.e., tobacco smoke.

- 1574 SOIL pH, RAINFALL AND DEATH RATES FOR ESOPHAGEAL CANCER IN CHILEANS. (E.) Zaldivar, R. (Tennessee Coll. Med., Memphis) and H. Robinson. *Beitr Path Bd* 151(3):317-321, 1974.

The relationship between the soil pH and esophageal cancer was analyzed in 21 Chilean provinces. There was a significant negative association between soil pH and the annual rainfall in soil samples taken from depths of 0-22 cm and 22-90 cm; the pH values from the samples taken from these depths were positively correlated. A significant positive correlation (0.738) was also found between the soil pH at 0-22 cm and the age-adjusted death rate for esophageal cancer. These data confirm the results of studies conducted along the northern coast of Iran, where high rates of esophageal cancer were associated with high silica levels in the soil.

- 1575 MULTIPLE PRIMARY NEOPLASMS IN BLACKS COMPARED TO WHITES. I. FURTHER CANCERS IN PATIENTS WITH HODGKIN'S DISEASE, LEUKEMIA, AND MYELOMA. (E.) Newell, G. R. (Natl. Cancer Inst., Bethesda, Md.), E. T. Krementz, J. D. Roberts and B. K. Kinnear. *J Natl Cancer Inst* 52(3):635-638, 1974.

Incidence of multiple primary neoplasms in patients with Hodgkin's disease, leukemia, and myeloma was determined from the 23-yr experience of the Charity Hospital Tumor Registry. Expected cancers were calculated by application of age-, sex-, and race-specific incidence rates to the person-years experience in the registry; these rates were compared with observed cancers. Whites with both Hodgkin's disease and leukemia had an increased risk for subsequent development of skin cancer, but this was thought due to artifacts of reporting. Blacks with leukemia had a significantly increased risk of later lung cancer. White males with myeloma had a 6.6-fold increased risk of subsequent cancer, and, although not statistically significant, this might be accounted for by subsequent cancer of the stomach.

- 1576 INCIDENCE AND HISTOPATHOLOGY OF MALIGNANCIES OF THE FEMALE GENITAL ORGANS IN THE UNITED STATES. (E.) Cramer, D. W. (Natl. Cancer Inst., Bethesda, Md.) *Am J Obstet Gynecol* 118(4):443-460, 1974

The incidence of morbidity from cancer of the female genital organs in the United States between 1969 and 1970 was determined using data from the Third National Cancer Survey. During this period, there were 20,855 newly diagnosed cancers of the female genital organs, 60% being invasive carcinomas. Of the invasive carcinomas, 38% originated in the corpus, 30% in the cervix, and 25% in the ovaries; 94% of the *in situ* carcinomas originated in the cervix. The incidence of cancers of the corpus and ovary was greater among white women, while cancers of the cervix were more common in black women. In both blacks and whites younger than 45 yr, cervical cancers were preponderant, cancers of the cervix remaining the most common malignancy of the female genital organs throughout life in blacks. In whites, cancers of the corpus and ovary increase rapidly in incidence in the 45-54-yr age group, the incidences of cancers of the cervix, corpus, and ovary being similar during this period. After age 55, cancers of the corpus and ovary were more common than those of the cervix among white women. In this survey 129 women had multiple primary cancers within the female genital tract and 278 women had a genital organ cancer and a nongenital organ cancer. The mean age of patients with *in situ* carcinomas was significantly less than that of patients with invasive cancers. The histopathologic types varied with age and race. Data from 1947 indicate a decrease in the crude rate for all invasive malignancies of the genital tract in women over 19, from 118 to 89 cases per 100,000. This reflects a decrease in the incidence of invasive cervical cancer, no significant changes having occurred in the other sites.

- 1577 FREQUENCY OF LYMPHORETICULAR TUMORS AND LEUKEMIAS IN JAPAN. (E.) Akazaki, K. (Aichi Cancer Ctr. Res. Inst., Nagoya, Japan) and H. Wakasa. *J Natl Cancer Inst* 52(2):339-343, 1974.

To determine the frequency of lymphoreticular tumors and leukemias in Japan. Five different sources of material were reviewed. The standardized death rates of malignant lymphomas by prefectures showed a north-to-south gradient of increasing rates for all three types of tumors: lymphosarcoma, reticulosarcoma, and Hodgkin's disease. The relative frequency studies revealed an extremely high frequency of reticulosarcoma compared with lymphosarcoma and Hodgkin's disease, male predominance in the sex ratio, and bimodality in the age distribution for lymphosarcoma. Reticulosarcoma and Hodgkin's disease showed the highest frequency in the seventh decade. The rarity of Burkitt's tumor in Japan was confirmed. Histologic classification of Hodgkin's disease showed that the nodular sclerosis type was less frequent in Japan than in the United States. Comparison of the periods 1958-1960 and 1967-1969 showed a distinct increase in Hodgkin's disease. Lymphocytic leukemia had a much lower frequency than myelocytic leukemia, and the rarity of chronic lymphocytic leukemia was particularly evident. All types of leukemia were rare after age 45.

- 1578 HISTOLOGY AND CELL PROLIFERATING IN HUMAN BLADDER TUMORS. AN AUTORADIOGRAPHIC STUDY. (E.) Hainau, B. (Finsen Inst., Dept. Path., Copenhagen, Denmark) and P. Dombernowsky. *Cancer* 33(1): 115-126, 1974.

The rate of cell proliferation (expressed as the potential doubling time (T_{pd}) of 70 bladder tumors of all degrees of differentiation, and of transitional epithelium from 19 patients without bladder tumors, was determined from the labeling index after the *in vitro* incorporation of 3H -thymidine and was compared with the histologic growth pattern and degree of epithelial anaplasia. The rate of cell proliferation in the bladder tumors increased significantly with increasing grade of histologic malignancy and was considerably compared with that of the normal bladder epithelium. Papillary tumors showed an increased rate of cell proliferation compared with that of intraepithelial and solid growths of the same degree of anaplasia. The discrepancy between the T_{pd} and the growth rate (known from clinical experience) is best explained in terms of extensive cell loss as a major parameter in the growth pattern of bladder tumors. The labeling pattern indicates that only a portion of the tumor cell population was proliferating. The nonproliferative pool has important therapeutic implications, since this fraction of the population is less sensitive to radiation and chemotherapy and is probably responsible for eventual relapse following treatment. This should be considered when using tumor regressing as a parameter for the efficiency of a therapy.

- 1579 MORTALITY AND MORBIDITY AMONG THE WORKING POPULATION OF ANTHOPHYLLITE ASBESTOS MINERS IN FINLAND. (E.) Meurman, L. O. (Dept. Path., U. Central Hosp. Kuopio, Finland). *Br J Ind Med* 31(2): 105-112, 1974.

The effects of anthophyllite asbestos on the mortality and morbidity rates among 1092 Finnish asbestos workers who were first employed in two mines between 1936 and 1969 were studied. Of the 95% of the workers who could be traced, 248 had died. A similar number of age-sex-matched controls was selected from a township about 60 km from the mines. The causes of death among the miners included an excess due to lung cancer and asbestosis, but cancers of the digestive system occurred in equal frequency among miners and controls, and neither group had any confirmed mesotheliomas. Assuming a multiplicative effect of asbestos and smoking, the relative risk of lung cancer was 17 times higher for an asbestos worker who smokes than for a nonexposed nonsmoker. Compared to the nonexposed nonsmoker, a smoker without asbestos exposure had a 12-fold greater chance of developing lung cancer and a non-smoking asbestos worker had a 1.4-fold greater risk. More heavy smokers were found among the asbestos workers than among the controls. Compared with the controls, the asbestos workers showed a threefold excess of dyspnea and a twofold excess of cough after adjustment for smoking. These results may underestimate the long-term effects of asbestos on the morbidity of the exposed population.

- 1580 MORTALITY EXPERIENCES AMONG TALC WORKERS: A FOLLOW-UP STUDY. (E.) Kleinfeld, M. (New York State Dept. Labor, Div. Ind. Hygiene, Brooklyn), J. Messite and M. H. Zaki. *J Occup Med* 16(5): 345-349, 1974.

Mortality statistics were analyzed among a group of 260 talc workers who had accumulated at least 15 yr of exposure to talc dust. There was a total of 108 deaths, the average at death being 60.3 yr. Malignancies of the lung and pleura accounted for 12% of these deaths, malignancies of the gastrointestinal tract and peritoneum accounted for 8.3%, and other types of malignancies accounted for 2.8%. The other deaths were attributed to cardiac problems, accidents or suicides, pneumoconiosis and its complications, and various other causes. The mean duration of exposure to talc dust among the 108 mortalities was 24.1 yr; the exposure was primarily to talc, tremolite, anthophyllite, carbonate dusts, and a small amount of free silica. The mortality rate from malignancies of the lung and pleura was approximately four times the expected rate, the significant increase occurring in the 60-79-yr age group. A significant decrease in the mortality rate from these malignancies in the period 1960-1969 (as compared with the period 1945-1959) indicates the effectiveness of various environmental controls instituted during this time. The mortality rate from other types of malignancies did not exceed expected values. The data indicate that the carcinogenic effect of commercial talc dust is manifested after exposure of 15 to 24 yr, and that very prolonged exposure (25 yr plus) does not appear to carry a significantly increased risk of cancer production.

- 1581 SEROEPIDEMIOLOGY OF HERPESVIRUS TYPE EPSTEIN-BARR IN BLOOD DONORS FROM COMMUNITIES AROUND LYON. (E.) Sohler, R. (Unit Virol., INSERM, Lyon, France), R. J. Freund, G. de-The, N. E. Day, A. Geser and G. Denhaut. *Am J Epidemiol* 99(6):414-424, 1974.

Five hundred and six blood donors between 18 and 60 yr of age, living in 25 different localities around Lyon, France, were studied serologically for 19 months to determine the epidemiology of antibodies to Epstein-Barr (EB) viral capsid antigen. The initial blood samples from each individual were used in cross-sectional analyses. About 85% of both males and females were definitely seropositive (titers above 1:10), although titers of 1:640 were more frequent in males than in females. There were substantial differences between villages both in terms of the percentage with clearly positive titers and in the geometric mean titers (GMT). In the villages with a large proportion of low titer sera, the GMT of the positive sera tended to be lower than the GMT of the positive sera in the villages with small proportions of low titers sera. These differences were not due to differences in age structure between the villages. Among those who were bled repeatedly, the titers remained stable over the 19 month period in 89%; among those whose titers varied, as many rose as fell. Episodes of illness between bleedings were slightly more frequent among those whose EBV titers changed, but no specific syndromes were associated with these changes.

- 1582 SEASONAL VARIATION IN ONSET OF BURKITT'S LYMPHOMA IN THE WEST NILE DISTRICT OF UGANDA. (E.) Williams, E. H. (Kuluva Hosp., Arua, Uganda), N. E. Day and A. G. Geser. *Lancet* (1971): 19-22, 1974.

Between 1961 and 1973, especially during the period 1966-73, a significant excess in the number of cases of Burkitt's lymphoma was recorded during the second half of each year in the West Nile District of Uganda. The incidence was 1.8 times higher in the second half of the year than in the first half. This seasonal effect was evident in each age-sex subgroup analyzed, and did not vary in relation to the localization of the tumor. While the seasonal effect was apparent in the central and south portions of the West Nile but not in the North, the season effect did not vary from east to west. These data point to the existence of an environmental factor which contributes to tumor causation after a relatively short latent period.

- 1583 CHRONIC CALCIFYING PANCREATITIS AND PANCREATIC CARCINOMA IN JAPAN. (E.) Ishii, K. (Hosp. Inst., Natl. Cancer Ctr., Tokyo, Japan), K. Nakamura, T. Takeuchi and T. Hirayama. *Digestion* 9(5):429-437, 1973.

Etiological and epidemiological studies were conducted in Japan using 150 patients with chronic calcifying pancreatitis and 1070 patients with carcinoma of the pancreas. The male-to-female ratio of calcifying pancreatitis was 3.5:1, while that of pancreatic carcinoma was 1.9:1. The frequency of both diseases was significantly lower among professional managing and service workers and significantly lower among agricultural workers. The cigarette smoking frequencies and daily intake of alcohol were significantly higher in both diseases than among a group of control subjects. Among the pancreatic carcinoma patients, the daily intake of meat, fish, milk, and soybean paste soup were also significantly higher, while the daily intake of rice, vegetables, and pickles was significantly lower than among the controls. The daily intake of alcohol was greater in calcifying pancreatitis than in pancreatic carcinoma. Alcohol abuse was the most important etiologic factor in calcifying pancreatitis, with alcohol abuse being closely correlated with pancreatic dysfunction in this group.

- 1584 INCIDENCE OF CHILDHOOD LEUKAEMIA. (E.) Freedman, L. (M. R. C. Statistical Res. Serv. Unit, London, England), N. A. Dent, C. Hunt, P. M. Payne and P. G. Smith. *Lancet* (1976):1059, 1974.

The incidence of childhood leukemia reported to three cancer registries in southern England was studied. The total population of children aged 0-14 yr exceeded 2.6 million. The rate of leukemia was statistically similar in the 0-4 and 5-14 age groups between 1971-1972. Although the incidence of leukemia was higher during this period than during the two preceding quinquennia, this difference was not statistically significant. While it is possible that there was an increase in the incidence of leukemia in 0-4-yr-olds in 1971-1972, the evidence is weak and further study is needed.

- 1585 OCCURENCE OF MALIGNANT MELANOMAS OF THE EYE AND THEIR DISTRIBUTION IN THE SOUTH MORAVIAN REGION WITHIN THE PERIOD OF 39 YEARS. (E.) Travnickova, V. (Inst. Pediatric Res., Brno, Czechoslovakia), M. Anton and M. Vrba. *Neoplasma* 21(1):119-124, 1974.

Between 1930 and 1968, 199 cases of malignant melanoma of the eye were registered in Czechoslovakia's South Moravian Region. There was no significant difference between the frequency of occurrence among males and females. The classical combinatorial analytical method was used to determine whether incidence rate varied with time and/or location. An hypothesized relationship between the incidence of this disease and the seasons of the year was not supported by the data. However, more females were affected through the middle of 1958, whereas more males were affected between the last half of 1958 and 1968; this difference was statistically significant. Similarly there was significant clustering according to location and quarters of the year. Thus it appears that the cases of malignant melanoma were not randomly distributed.

- 1586 KINETICS OF CELL PROLIFERATION IN SLOWLY GROWING, HIGHLY DIFFERENTIATED MOUSE HEPATOMA. (Rus.) Gel'shtein, V. I. (Inst. Exp. Clin. Oncol., Moscow, USSR) and L. B. Klempner. *Vopr Onkol* 19(12):41-46, 1973.

Mitosis and the tumor doubling time were investigated in hepatoma 48 which had been transplanted into C3HA mice by s.c. injection of a suspension of cells from the 34th or 35th mouse passage. Tumors appeared after 1-1.5 months. In 16 of the 17 tumors the tumor diameter increased linearly with time for 16-77 days. These 16 tumors grew at rates of 0.017 to 0.044 cm/day. The tumor doubling time increased from 7 days, when measurements were first made, to 21 days by 110-130 days after transplantation. The average doubling time for tumors measuring 0.2 cm in diameter was calculated to be 1.5 days. By autoradiography with ^3H -thymidine, the duration of the G_2 phase was calculated to be 2-2.5 hr and the duration of DNA synthesis, 9-12 hr. The labeling index, determined 1 hr after injection of ^3H -thymidine, was almost the same for all tumors (9.6-17.4%), and the ratio of the growth fraction to the duration of the mitotic cycle remained unchanged. The potential doubling ranged from 55-75 hr and remained unchanged when no evidence of cell necrosis was observed. No appreciable difference was found between the labeling index for cells in the stroma and for those in the capsule of the tumor. It is concluded that increased tumor doubling time is largely due to increased cell loss rather than to an increase in the duration of the mitotic cycle or a decrease in the fraction of proliferating cells. The loss factor increased from 0 to 0.9 in one generation, i.e. 90% of the proliferating cells were eventually lost after each mitotic cycle. This agrees with the finding that the greater the extent of cell differentiation, the more sensitive a tumor becomes to environmental factors causing cell necrosis. It is suggested that for slowly growing tumors, tumor growth could be halted or tumor regression obtained just as effectively by the use of agents which increase the percentage of necrotic cells as by the use of agents which interfere with mitosis.

1587 BLADDER TUMOURS AND OCCUPATION: A CORONER'S NOTIFICATION SCHEME. (E.) Veys, C. A. (North Staffordshire Inst. Res. Unit, Stoke-On-Trent, England). *Br J Ind Med* 31(1):65-71, 1974.

The coroner's office of the British borough Stoke-on-Trent recorded all cases of bladder cancer occurring within the borough between 1965 and 1970 and obtained complete occupational histories on each case reported. The occupational histories were then related to two industrial checklists: A, on which were listed occupational groups in which an increased incidence of cancer could be linked to known causative factors; and B, on which were listed occupational groups in which a statistical association has only been postulated. Among men with bladder tumors, 18% had worked in occupations listed on checklist A, while 16% had worked in occupations listed on B. Among the females with bladder tumors, 12% had worked in occupations on checklist A, while none had worked in occupations on B. The reported number of persons with bladder tumors did not exceed statistical expectations. Although in 1/3 of the persons with suspicious occupational histories, the working environment could be directly and realistically implicated in the development of bladder cancer. The study supports the view that the importance of occupational factors in the etiology of bladder tumors has hitherto been underestimated.

1588 CANCER OF THE COLON AND RECTUM VS. CANCER OF THE STOMACH AND ESOPHAGUS IN JAPAN - STATISTICAL REVIEW. (E.) Shindo, K. (Surg. Dept., Osaka U. Hosp., Japan). *Am J Proctol* 25(3):45-58, 1974.

In Japan in 1970, 4717 people died of cancer of the rectum, 3818 died of cancer of the colon, 36 died of cancer of the anus, 48,832 died of cancer of the stomach, and 4823 died of cancer of the esophagus. Mortality from cancer of the large intestine is increasing in this country, while mortality from cancer of the stomach is decreasing. The incidence of these cancers is slightly to considerably greater among men than women. Cancer of the rectum is most common in 65-69-yr-old men and 70-74-yr-old women, with cancers of the stomach and esophagus showing the same distribution. Cancers of the colon and rectum metastasized most frequently to the liver and lung. The most common form of treatment for both rectal and colonic cancer is surgical excision, followed by the use of anticancer agents, radiation therapy, and steroid therapy. Compared with other countries, the incidence of colonic cancer is low in Japan, while the incidence of rectal cancer is average.

1589 EPIDEMIOLOGIC AND PEDIGREE STUDY OF THE OCCURRENCE OF LYMPHOSARCOMA FROM 1953 TO 1971 IN A CLOSED HERD OF JERSEY COWS. (E.) Cypess, R. H. (Grad. Sch. Pub. Hlth., U. Pittsburgh, Pa.), J. H. Waller, C. K. Redmond, R. J. Tashjian and A. I. Hurvitz. *Am J Epidemiol* 99(1):37-43, 1974.

A retrospective study of a herd of approximately 240 Jersey cows with a high incidence of lymphosarcoma was conducted between 1953 and 1971. During this

period, there were 19 confirmed cases of lymphosarcoma, the death rate from this disease being 7.9%. If only those cows surviving 6 years or more were considered, the death rate from lymphosarcoma was approximately 21.6%. Pedigree analysis for familial aggregation indicated clustering of incidence by sire groups and cow families, but exact analysis for temporal clustering was not possible. The mode of transmission did not suggest a simple Mendelian mode of inheritance, although this possibility cannot be ruled out. This herd provides an excellent source of data for prospective studies on the etiology and nature of lymphosarcoma.

1590 TUMORS OF THE NASOPHARYNX IN TUNISIA: AN ANATOMIC AND CLINICAL STUDY BASED ON 143 CASES. (E.) Cammoun, M. (Nat'l. Cancer Inst., Tunis, Tunisia), G. V. Hoerner and N. Mourali. *Cancer* 33(1):184-192, 1974.

Between 1969 and 1971, 102 males and 41 females with nasopharyngeal cancer were observed and treated at the National Cancer Institute in Tunisia. The average age for men was 44.6 yr and that for women was 42.7 yr. The peak incidence was in the 50-59-yr age group for both sexes, with a smaller peak in the 10-19-yr age group. The general incidence of nasopharyngeal cancer in Tunisia is estimated to be about 2.05 cases per 100,000 population. The incidence of nasopharyngeal tumors increases with population density in Tunisia. The average period of time between tumor manifestation and seeking of medical care was 8 months. The most frequent clinical signs were cervical adenopathy, epistaxis, nasal obstruction, auditory problems, and neurologic disorders. Fungiform tumors made up about 81% of the series; only 11 cases showed infiltration or ulceration. There were two adenocarcinomas, six hematosarcomas, and one plasmocytoma. A type of herpes virus may be involved in the etiology of nasopharyngeal cancer.

1591 BREAST FEEDING, FAMILY HISTORY, AND BREAST DISEASE. (E.) Morgan, R. W. (Dept. Preventive Med., U. Toronto, Canada) D. V. Vakil and M. L. Chipman. *Am J Epidemiol* 99(2):117-122, 1974.

A retrospective cohort study of 1595 women over 60 years of age and 1701 daughters of these women was undertaken to determine the relationship between breast feeding and benign and malignant breast disease among the offspring. Since the breast-fed women had a breast cancer experience remarkably similar to that of the women who were never breast fed, there is no evidence to support the hypothesis that the risk of breast cancer is related to the experience of being breast fed. Likewise, breast feeding does not appear to influence the risk of developing benign breast disease. The daughters of breast cancer patients appear to have an increased risk of developing breast cancer and/or benign breast disease. In such familial cases, both diseases tend to appear earlier than individuals with no family history of breast disease. Benign breast disease in the mother may increase the risk of breast cancer in the daughter.

- 1592 CELL POPULATION GROWTH IN CHRONIC MYELOID LEUKEMIA. (E.) Gavosto, F. (Div. Haematol., Med. Clin., U. Turin, Italy). *Haematologica* 57(11):663-671, 1973.

Kinetic studies of human chronic myeloid leukemia (CML) cell proliferation patterns indicate that: the labeling indexes of proliferating cells in CML are lower than in the normal subject; the generation times are longer in CML; the proliferation rate values for each subcompartment are lower in CML; cell flow values are lower in CML; circulating granulocyte values are very much higher in untreated patients; and the total granulocyte pool, and hence its absolute turnover rate, are above normal. Thus, in CML the extraordinary increase in cell production is not simply a result of enhanced specific proliferation on the part of granulopoietic cells actually present, although the initial transformation in leukemia must occur in stem cells of the same kind which feed normal hematopoietic tissues. The unlimited growth potential in CML is then entirely dependent on progressive enrichment of the stem cell pool. Like normal stem cells, those of leukemia probably have different levels of proliferative potentiality, but the leukemic population develops and increases its size continuously. Moreover, its stem or clonogenic cells are no longer sensitive to regulating factors, although they are not unaffected by the size of the population. Even though negative values may occasionally be induced by treatment, the overall growth trend will always be positive as a result of the innate ability of the leukemic stem cells to augment their own pool.

- 1593 THE DISTRIBUTION OF INCUBATION PERIODS OF NEOPLASTIC DISEASES. (E.) Armenian, H. K. (Johns Hopkins U., Sch. Hygiene Pub. Hlth., Baltimore, Md.) and A. M. Lilienfeld. *Am J Epidemiol* 99(2):92-100, 1974.

The literature was reviewed for neoplastic diseases with some known etiologic factors and specific exposure times in an effort to estimate the distribution of incubation periods. An attempt was then made to apply Sartwell's model of the distribution of incubation periods in infectious diseases (i.e., the logarithms of incubation times in infectious diseases are approximately normally distributed for diseases of both short and long incubation periods) to the distribution of incubation periods in several selected neoplasms (radiogenic leukemias, thyroid cancer, thyroid adenomas, Wilms' tumor, bladder tumors, and lung cancer following occupational exposure to carcinogens). For these neoplasms, most of the observations approximate a logarithmic normal distribution. Four different sets of observations on radiogenic leukemias, although collected from different populations and under different conditions, had estimated median incubation periods and dispersion factors that were quite similar. The distribution of latent intervals between the last dose of chloramphenicol and the first manifestation of pancytopenia fits the log normal pattern also and points out the potential in generalizing from Sartwell's model to other chronic diseases.

- 1594 EPIDEMIOLOGICAL FOLLOW-UP STUDIES OF THE PORTUGUESE THOROTRAST SERIES (UP-DATED RESULTS). (E.) da Silva Horta, J. (Inst. Pathol., Fac. Med., U. Lisbon, Portugal), L. Cayolla da Motta and M. H. Tavares. *Proceedings Third Int. Meeting Toxicity Thorotrast (April)* 193-211, 1973.

Of 2,500 Portuguese patients known to have been injected (primarily for cerebral angiographies) with Thorotrast between 1930 and 1955, 51% were followed up until the end of 1972. A partial control group of patients matched for age, sex, and general type of disease, but injected with a nonradioactive control drug, was also followed up. In comparison with the controls, the Thorotrast subjects have shown a gross excess of malignancies and of severe fibrosis of the liver and the tissues around the blood vessels when the drug had been spilled and retained during intravascular administration. The excess malignancies were primarily leukemias and other rapidly fatal blood dyscrasias and liver tumors, particularly hemangioendotheliomas. There was also a slight excess of lung cancer among the Thorotrast population. The high incidence of blood dyscrasias probably represents a radiation induced or precipitated condition or group of conditions. The data indicate that Thorotrast, when retained in the human body, is capable of inducing local fibrosis at the area of accumulation and, in some cases, malignant change after several years.

- 1595 AN EPIDEMIOLOGIC STUDY OF THE RELATIONSHIP OF REPRODUCTIVE EXPERIENCE TO CANCER OF THE OVARY. (E.) Joly, D. J. (Johns Hopkins U. Sch. Hygiene Pub. Hlth., Baltimore, Md.), A. M. Lilienfeld, E. L. Diamond and I. D. J. Bross. *Am J Epidemiol* 99(3):190-209, 1974.

Between 1957 and 1965, over 400 cases of ovarian cancer were admitted to the Roswell Park Memorial Institute in Buffalo, New York. These cases were compared with other cancers and nonneoplastic diseases in terms of demographic and social attributes, family history, radiation exposure, menstrual and reproductive characteristics, and personal habits. In comparisons with the controls, the ovarian cancer group showed: a lower mean number of pregnancies, even when pregnancy rates were calculated per 1000 person-years at risk of the event, a larger proportion of never-pregnant and ever-pregnant women; an increase in the relative risk of cancer of the ovary as the total number of pregnancies decreased; a greater risk of ovarian cancer in every married-never pregnant women, as compared with never-married women; a late age at first pregnancy, except in comparison with breast cancer controls; a greater interval between first marriage and first conception; a greater difference compared to their mothers is completed sibship size; a larger proportion of women who had tried and failed to become pregnant at least once; and an increase in the frequency of miscarriages. These data suggest that women who developed ovarian cancer had a gonadal status which predisposed them to both ovarian cancer and low fertility.

1596 EPIDEMIOLOGICAL INVESTIGATION ON STOMACH
 CANCER MORTALITY IN CHILEANS: ASSOCIATION
WITH NITRATE FERTILIZER. (E.) Zaldivar, R. (Tennes-
see Coll. Med., Memphis) and H. Robinson. *Z Krebs-
forsch* 80(4):289-295, 1973.

The relationships between age-adjusted gastric cancer mortality rates in the various Chilean provinces and the following variables were studied by multivariate analysis: exposure to sodium nitrate; rainfall; and latitude. The stomach cancer death rate and exposure to sodium nitrate (metric tons of nitrate per person) were significantly correlated. While the relative proportion of miners was not significantly associated with the provincial death rate, the relative proportion of farmers was significantly correlated. Thus, it may be the farmers in contact with large amounts of nitrate fertilizer who primarily influence the mortality rates. However, miners have a higher mortality risk from stomach cancer than farmers. This finding may be explained on the basis of the known associations between iron dust and stomach cancer as well as between coal mining and gastric cancer. The three variables studied here accounted for only 44% of the variability in mortality rates from gastric cancer, indicating that there are other factors which influence the mortality rates.

1597 FAMILIAL MEDULLARY CARCINOMA OF THE THYROID.
(E.) Anonymous. *Br Med J* 2(5917):461, 1974.

Medullary carcinoma of the thyroid is a tumor of the parafollicular or C cells, which produce calcitonin. It is inherited as an autosomal dominant with a high degree of penetrance. It is associated with pheochromocytomas, parathyroid hyperplasia or adenomas, and occasionally with Cushing's syndrome. It should be standard practice to investigate the families of patients with the medullary carcinomas of the thyroid syndrome. The most accurate screening test for the presence of the disease is measurement of calcitonin in the peripheral circulation; a raised serum level of calcitonin in a patient with the familial syndrome with or without mucosal neuromas is an indication for total thyroidectomy after careful exclusion of a pheochromocytoma. In some people the basal calcitonin level is normal, but a test using calcium infusion to stimulate calcitonin secretion may produce an abnormality. Patients at risk who have normal basal calcitonin levels and a normal response to calcium should have annual calcium infusion tests performed. If the process is found during the early, preinvasive stages, total thyroidectomy should prove curative.

1598 COLON CANCER AND BLOOD-CHOLESTEROL. (E.)
 Rose, G. (St. Mary's Hosp. Med. Sch., London,
England), H. Blackburn, A. Keys, H. L. Taylor, W. B.
Kannel, O. Paul, D. D. Reid and J. Stamler. *Lancet*
(7850):181-183, 1974.

Based on the hypothesis that within a population the level of blood cholesterol should predict the risk of colon cancer, data from six prospective surveys of coronary heart disease were studied. These studies provide data on a total of 90 cases of fatal colon

cancer among male patients whose average age at death was 52.39 ± 6.88 yr. The initial levels of blood cholesterol in these men were significantly lower than the expected values, the median deviation being -0.26 standard deviation units (corresponding to a little more than 10 mg/100 ml). This tendency was not significantly correlated with the interval from screening to death, nor was it shared by cases involving other alimentary carcinomas. It is possible that within the populations studied, individuals with lower levels of blood cholesterol may tend to form more bile salts, which would increase the amount of substrate available for the carcinogen-forming bacteria. It is also possible that the negative association between blood cholesterol and colon cancer might arise due to the extensive colonization of the intestine with bile-degrading bacteria which utilize blood cholesterol.

1599 EPIDEMIOLOGY OF CANCER OF THE RENAL PEL-
 VIS AND URETER. (E.) Schmauz, R. (Med.
Sch., Lubeck, W. Germany) and P. Cole. *J Natl Cancer
Inst* 52(5):1431-1434, 1974.

Forty-three persons with cancer of the renal pelvis or ureter were compared with 509 persons with cancer of the bladder and with controls drawn from the population of the study area. Data were gathered by at-home interviews. Cancers of all three sites occur predominantly in men and in old age. Increased risk of bladder cancer is associated with low exposure to cigarette smoking, coffee drinking, and leather work. For cancers of the renal pelvis and ureter, excess risk is found only for high levels of exposure. The rapid transit of carcinogens through the renal pelvis and ureter may explain the association of cancer at these sites with only high-level exposures. Population attributable risks (i.e., the proportion of the disease that could be prevented if the exposure studied were a cause and if it were stopped) were computed for each exposure. It is estimated that 38.8% of the cases of cancer of the renal pelvis and ureter in men is attributable to cigarette smoking, 45.0% to coffee drinking, and 4.7% of the cases in men and women to the occupation of leather working. The values for bladder cancer are 41.0, 26.6, and 2.4%, resp.

1600 CANCER OF THE CERVIX: A SEXUALLY TRANSMIT-
 TED INFECTION? (E.) Beral, V. (Dept. Med.
Statistics Epid., London Sch. Hygiene Tropical Med.,
England). *Lancet* (7865):1037-1040, 1974.

Two hypotheses have been proposed to explain the etiology of cervical cancer: (1) During adolescence, the cervical epithelial cells are especially vulnerable to carcinogens such as chronic cervicitis, hormonal imbalance, smegma, trauma, coal-tar douches, and sperm DNA; and (2) malignant change is induced by a sexually transmitted infection, possibly the herpesvirus type II. When mortality patterns for cancer of the uterine cervix were compared with trends in the incidence of sexually transmitted diseases in England, Scotland and Wales, there were striking associations between the temporal, social class, occu-

pational, and geographic distributions of these diseases. The data suggest that exposure to sexually transmitted infection is an important determinant in the etiology of cervical cancer. The data do not support the hypothesis that the cervical cells are particularly sensitive to carcinogens during adolescence. Although they are still young, women born after 1940 are already experiencing increased mortality from cervical cancer. If cervical-cancer prevention and therapy remain unchanged, this generation's high risk of death from this disease will probably continue to operate throughout their lives.

- 1601 TWO-YEAR SURVEY OF HEMATOLOGIC MALIGNANCIES IN UGANDA. (E.) Amsel, S. (U. Maryland Hosp., Baltimore) and J. S. Nabembezi. *J Natl Cancer Inst* 52(5):1397-1401, 1974.

All cases of leukemia, lymphosarcoma, Burkitt's lymphoma, Hodgkin's disease, multiple myeloma, and histiocytic medullary reticulosis reported in Uganda during a 2-yr period (1971-1972) were analyzed with regard to sex, incidence, and regional variations in incidence. In Kyadondo County, the incidence of these diseases was similar to that found in other African populations, but lower than the rates found in Western countries. In the age-specific incidence curves for Uganda, a marked decrease in incidence in the older age group was evident at a point where the rate in Western countries increases geometrically. An exception was Hodgkin's disease, for which the rate and bimodal shape of the age-specific incidence curve were similar to those of Western countries. There was a low rate of leukemia of all cytologic types, due possibly to underdiagnosis. In the Northern Province of Uganda, the high rate of Burkitt's lymphoma was confirmed, and the incidence of Hodgkin's disease and lymphosarcoma was higher than expected for a rural area. This observation could have implications as to the specificity of lymphomas associated with regions of hyperendemic malaria. Eleven cases of histiocytic medullary reticulosis were recorded. The reason for this high rate is not known.

- 1602 CANCER MORTALITY AMONG CHINESE AMERICANS, 1950-69. (E.) Fraumeni, J. F., Jr. (Natl. Cancer Inst., Bethesda, Md.) and T. J. Mason. *J Natl Cancer Inst* 52(3):659-665, 1974.

During 1950-1969, 5713 deaths among Chinese in the United States were attributed to cancer. The total cancer mortality rate among Chinese males was significantly higher ($P < 0.01$) than that of white males in the United States, but comparable to that of black males, whereas the corresponding rate among Chinese females was significantly lower ($P < 0.01$) than that of both white and black females. Compared with whites and blacks, mortality from nasopharyngeal cancer was elevated 26-fold in Chinese males and 22-fold in Chinese females, with declining rates during the study interval. Mortality from primary liver cancer and lung cancer, particularly in females, was also significantly high among Chinese. Thyroid cancer mortality was excessive in Chinese of both

sexes, but significant only in males. On the other hand, significantly low mortality was reported among Chinese males for prostate and bladder cancers, and among Chinese females for breast and cervical cancers. Mortality from cancers of the large intestine and rectum in Chinese was excessive in males, but low in females. The mortality patterns by cancer site among Chinese generally agree with cancer incidence statistics in Hawaii and California and suggest shifts away from the cancer risks among Chinese in Asia and toward those prevailing in the general population in the United States.

- 1603 A RETROSPECTIVE CASE-CONTROL QUESTIONNAIRE STUDY OF HODGKIN'S DISEASE MORTALITY AND OCCUPATIONAL EXPOSURE TO WOOD AMONG WHITE MALES OVER AGE 19, WASHINGTON STATE: 1965-1970. (E.) Petersen, G. R. (U. Washington, Seattle). *Diss Abs Int B* 35(1):364, 1974.

- 1604 LEUKEMIA IN PEDIATRICS: CONSIDERATION OF 454 CASES OBSERVED AT THE CHILDREN'S HOSPITAL, BUENOS AIRES, IN A TEN-YEAR PERIOD (1961-1970). (Sp.) Sackmann Muriel, F. (Children's Hosp., Buenos Aires, Argentina), J. L. Braier and J. A. Penalver. *Sangre* 18(2):201-214, 1973.

- 1605 GROWTH QUANTITATION OF HUMAN MAMMARY CARCINOMA IN ORGAN TISSUE CULTURE. (E.) Aspegren, K. (Dept. Surg., U. Lund, Sweden) and H. Danielsson. *Am J Surg* 128(1):42-48, 1974.

- 1606 FAMILIAL CANCER OF THE KIDNEY AND THE HLA SYSTEM. FOUR CARCINOMAS OF THE LEFT KIDNEY IN ONE SIBSHIP. (Fr.) Valleteau de Moulliac, M. (No affiliation), R. Ganansia, J. Hors, A. Letexier and M. Morin. *Nouv Presse Med* 3(24):1539-1543, 1974.

- 1607 CERVICAL CANCER DETECTION IN JAMAICA. CYTOLOGIC SCREENING OF A SAMPLE POPULATION. (E.) Persaud, V. (Dept. Pathol., U. West Indies, Kingston, Jamaica). *Int J Gynaecol Obstet* 12(4):151-155, 1974.

- 1608 THE INCIDENCE OF LEUKAEMIA IN THE RHODESIAN AFRICAN - A FIVE YEAR HOSPITAL SURVEY. (E.) Lowe, R. F. (Harare Central Hosp., Salisbury, Rhodesia). *Cent Afr J Med* 20(4):80-84, 1974.

- 1609 ESOPHAGEAL CANCER IN FRANCE: INCREASED RISK. (Fr.) Lambert, R. (Edouard Herriot Hosp., Lyon, France) and J. C. Audigier. *Nouv Presse Med* 3(26):1647-1648, 1974.

- 1610 NUCLEO-CYTOPLASMATIC CONSTANTS OF MALIG-NIZED STRUCTURES. (Rus.) Gelfandbein, Y. A. (No affiliation), B. L. Kaplan and I. M. Maerovich. *Eksp Khir Anesteziol* (3):3-9, 1973.

1611 EQUATIONS OF DYNAMICS OF TRANSFORMATION OF NUCLEO-CYTOPLASMATIC CONSTANTS DURING THE PROCESS OF MALIGNIZATION OF EPITHELIAL FIELDS. (Rus.) Gelfandbein, Y. A. (No affiliation), B. L. Kaplan and I. M. Maerovich. *Eksp Khir Anesteziol* (4):35-38, 1973.

1612 CORRELATIONS BETWEEN THE DNA CONTENT DISTRIBUTION AND TRITIATED THYMIDINE STUDIES IN RELATION TO POPULATION SIZE IN SARCOMA 180 *IN VITRO*. (E.) Shackney, S. E. (Natl. Cancer Inst., Bethesda, Md.) and S. S. Ford. *Cancer Res* 34(6):1401-1407, 1974.

1613 QUANTITATION OF TOTAL-BODY TUMOR CELLS (MOPC 104E). II. ASCITES TUMOR MODEL. (E.) Hiramoto, R. N. (U. Alabama Med. Ctr., Birmingham), V. K. Ghanta and N. M. Hamlin. *J Natl Cancer Inst* 53(3):767-771, 1974.

1614 KINETICS OF HUMAN MAMMARY CARCINOMAS AND THEIR CORRELATION WITH THE CANCER AND THE HOST CHARACTERISTICS. (E.) Silvestrini, R. (Natl. Inst. Study Cure Tumors, Milan, Italy), O. Sanfilippo and G. Tedesco. *Cancer* 34(4):1252-1258, 1974.

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1616 CANCER OF THE HEAD AND NECK IN UTAH. (E.) Smart, C. R. (Latter-Day Saints Hosp., Salt Lake City, Utah), J. L. Lyon, M. Skolnick, M. L. Wilson, C. B. Edwards and L. R. Cowan. *Am J Surg* 128(4):463-465, 1974.

1617 THE FAMILIAL ASSOCIATION OF NEUROFIBROMATOSIS, PERONEAL MUSCULAR ATROPHY, CONGENITAL DEAFNESS, PARTIAL ALBINISM, AND AXENFELD'S DEFECT. (E.) Bradley, W. G. (Newcastle U. Hosp. Group, England), J. Richardson and I. J. C. Frew. *Brain* 97(3):521-532, 1974.

1618 CANCER OF THE ENDOLARYNX. ANALYSIS OF 415 CASES. (E.) Gregoriades, G. (Cancer Inst., Theagenion Mem., Thessaloniki, Greece). *J Laryngol Otol* 88(8):749-757, 1974.

1619 RETINOBLASTOMA IN NORWAY. (E.) Horven, I. (Dept. Ophthalmol., U. Oslo, Norway). *Acta Ophthalmol (Suppl) (Kbh)* 123:103-109, 1973.

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1621 RECENT STUDIES OF PERSON-PERSON TRANSMISSION OF HODGKIN'S DISEASE. (E.) Smith, P. G. (DHSS Cancer Epidemiol., Clin. Trials Unit, Oxford U., England). *Proc R Soc Med* 67(7):683-684, 1974.

1622 CANCER OF THE COLON IN SOUTH AFRICAN POPULATIONS. THE BEARING OF ROUGHAGE, BOWEL MOTILITY AND THE CHEMICAL AND BACTERIAL COMPOSITION OF FAECES. A PROGRESS REPORT. (E.) Walker, A. R. P. (South African Inst. Med. Res., Johannesburg). *S Afr Cancer Bull* 17(4):159-161, 1973.

1623 FAMILIAL POLYPOSIS OF THE COLON. (E.) Torrington, M. (Med. Sch., Cape Town, South Africa). *S Afr Cancer Bull* 17(4):156-158, 1973.

1624 IMMUNOLOGICAL DEPLETION CONTRIBUTING TO FAMILIAL HODGKIN'S DISEASE. (E.) Fenelly, J. J. (St. Vincent's Hosp., Dublin, Ireland) and A. McBride. *Br J Cancer* 30(2):182, 1974.

See also:

- * (Rev): 1218, 1220, 1222
- * (Chem): 1339

- 1625 ERYTHROKINETICS IN MYELOPROLIFERATIVE SYNDROMES. (Ger.) Meuret, G. (Med. Clin., U. Freiburg, Germany), D. Gehring and G. Hoffmann. *Radiobiol Radiother (Berl)* 14(1):61-71, 1973.

Using double labeling with ^{59}Fe and ^{51}Cr , erythrokinetic investigations were performed on patients with myeloproliferative syndromes of varying degrees of severity. Patients consisted of three with polycythemia vera, four with chronic myeloid leukemia, eight with osteomyelofibrosis, and two with unclassified myeloproliferative syndromes. In the initial stages of polycythemia vera and unclassified myeloproliferative syndromes, the production of RBC in the bone marrow increased. Erythropoiesis decreased in the bone marrow but occurred in the spleen and liver in the later stages of these diseases. Anemia resulted from a decrease in RBC survival and hemolysis in the spleen. In terminal cases, erythropoiesis even occurred in the lymph nodes. Iron turnover in the plasma was increased in 11 patients and ^{59}Fe utilization was reduced in 7 in advanced stages of myeloproliferative diseases. This was traced to inefficient extramedullary hematopoiesis in 3 cases, but extramedullary hematopoiesis was more or less efficient in three-fourths of the patients studied. Hepatic erythropoiesis was adequate enough to maintain a normal RBC in a splenectomized patient with aplastic medullary hematopoiesis. Erythropoiesis ceased completely during the myeloblast crisis in terminal stages of chronic myeloid leukemia. This condition, which can occur in all myeloproliferative syndromes, is acute leukosis. It is characterized by the almost complete absence of differentiated blood-forming cells and almost exclusive production of atypical cells.

- 1626 ELECTRON MICROSCOPY IN THE STUDY OF MALIGNANT LYMPHOMAS. (E.) Ishikawa, E. (Jikei U. Sch. Med.) and H. Yasuda. *Gann Monograph on Cancer Res* 15:293-304, 1973.

The morphological features of the following malignant lymphomas were studied: lymphosarcoma, reticulum cell sarcoma, Burkitt's lymphoma, and Hodgkin's disease. Cells composing the lymphosarcomas are either well differentiated, poorly differentiated, or an admixture of both. The proliferation of tumor cells results in a change in the cell population with only minimal destruction of the lymph node architecture. The differentiated reticulum cell sarcoma is characterized by lysosomal figures and some degree of development of the rough endoplasmic reticulum; such changes are seldom seen in the undifferentiated type. Reticular fibers closely related to tumor cells appear both on the surface and engulfed. The Reed-Sternberg in Hodgkin's disease show characteristic features suggestive of reticulum cell origin. The basic structure of the lymph node is greatly altered in these cases. The morphological features of the primary Burkitt's lymphoma cells are similar to those of the poorly differentiated lymphocytic series (lymphoblasts). Large irregularly shaped cells of histiocytic origin are found intermingled among the tumor cells in Burkitt's lymphoma, although they are presumably nonneoplastic.

- 1627 ULTRASTRUCTURE AND SECRETION OF HUMAN SOMATOTROPIC ADENOMAS IN TISSUE CULTURE STUDIED WITH ^3H -LABELED LEUCINE. (Fr.) Peillon, F. (Fac. Med. Pitie-Salpetriere, Paris, France), M. Gourmelen, M. Donnadieu, A. Brandi and M. T. Pham Huu Trung. *Ann Endocrinol (Paris)* 34(6):728-733, 1973.

Somatotropic adenomas were removed from ten patients with acromegaly, and tumor slices were cultured in medium 199 containing 20% fetal calf serum and 2000 U/ml penicillin. Morphological studies were performed every seven days for one month. Explants tended to become round in the first 48 hr after they were placed in culture, and by the end of cultivation their volume had decreased by one-half. A central zone of necrosis was surrounded by layers of living cells. During cultivation a continuous decrease occurred in the number of granules secreting human growth hormone (HGH), while the number of lysosomes gradually increased. By radioimmunological assays, it was demonstrated that HGH concentrations were ten times higher in adenoma cultures than in cultures of normal pituitaries. HGH secreted by the adenomas reacted in the same way as standard HGH in a radioimmunological assay and gave an elution curve which could be superimposed on that of standard HGH when it was subjected to chromatography on Sephadex G 100. Anti-HGH antibodies used in the radioimmunoassay reacted with HGH secreted by the adenomas but not with standard ovine prolactin. In some cultures the rate at which HGH was secreted was at least equal to the rate of secretion by the original tumor (2250 ng/mg tumor tissue). After 48 hr, 13% of ^3H -leucine added to the culture medium had been incorporated into protein in the medium. By using anti-HGH antibodies absorbed on solid particles, it was demonstrated that 40.4% of these proteins consisted of HGH.

- 1628 SPONTANEOUS TUMORS IN SPRAGUE-DAWLEY RATS AND SWISS MICE. (E.) Prejean, J. D. (Southern Res. Inst., Birmingham, Ala.), J. C. Peckham, A. E. Casey, D. P. Griswold, E. K. Weisburger and J. H. Weisburger. *Cancer Res* 33(11):2768-2773, 1973.

A spontaneous tumor incidence of 45% was noted in 360 Sprague-Dawley rats (179 males and 181 females) and a 26% incidence was seen in 254 Swiss mice (101 males and 153 females) used as untreated control animals in an 18-month series of carcinogenesis experiments. The percentage of female rats with tumors was almost double that of males, the difference being accounted for chiefly by the high incidence of mammary tumors in the females. The largest number of rat tumors occurred in the endocrine system, mainly the pituitary and adrenal glands, with females exhibiting a higher incidence than males. There were no liver tumors. The largest group of mouse tumors occurred in the pulmonary system, with a higher incidence in females than in males. Urinary system tumors were observed in the males but not in the females. Tumors of the integument, reproductive organs, and the reticuloendothelial and lymphatic organs were also observed.

1629 CHROMOSOMAL BANDING PATTERNS AND *IN VITRO* TRANSFORMATION OF SYRIAN HAMSTER CELLS.

(E.) DiPaolo, J. A. (Nat'l. Cancer Inst., Bethesda, Md.), N. C. Popescu and R. L. Nelson. *Cancer Res* 33(12):3250-3258, 1973.

Chromosome banding techniques were used to analyze the chromosomal constitution of hamster cells transformed by chemical carcinogens and fibrosarcomas obtained after injection of the transformed cell lines. Each transformed line is considered unique because each was derived from fetal material from a different pregnant animal. The chromosome modes of the transformed lines and tumors were generally near-diploid. Analysis of bands verified the occurrence of identical banding patterns in the marker chromosomes of transformed lines and tumor-derived cultures, thus providing unequivocal evidence that the fibrosarcomas were produced by the cells that were transformed *in vitro* and making it possible to recognize 10 marker chromosomes and their origin. Different carcinogens may produce transformations associated with the same specific marker, but not all transformed lines have the same markers even with the same chemical carcinogen. One marker, M₁, which was observed most frequently in the transformed lines and tumor cell cultures, was found in one case in a tumor-derived culture but not in the parental transformed line. The same marker was also found to occur in late passages of certain transformed lines and tumor cultures even when it had not been present in earlier passages. This suggested that the observed chromosomal changes were secondary. The question whether chromosome changes are causal factors in carcinogenesis thus remains unanswered.

1630 LYMPHOID CELLS IN CARCINOMA OF THE BREAST: FAILURE OF RESPONSE TO PHYTOHAEMAGGLUTININ

IN VITRO. (E.) Blomgren, H. (Radiumhemmet, Karolinska Sjukhuset, Stockholm, Sweden), U. Glas, S. Franzen and P.-O. Granberg. *Acta Radiol [Ther]* Stockh 12(5):434-442, 1973.

Cells obtained from four mammary carcinomas showing cytologic signs of extensive lymphocyte infiltration were cultured in media containing penicillin, streptomycin and human serum. Phytohemagglutinin was added to half of the cultures, and, after 3 days, ¹⁴C-thymidine was added to all of the cultures. The lymphoid cells infiltrating the tumors exhibited an extremely low capacity to respond to phytohemagglutinin as compared with autochthonous blood lymphocytes. Since phytohemagglutinin is considered to have a high specific mitogenic effect on T-cells, cells other than T-cell may have almost selectively invaded the tumors. The cells did not appear, however, to have been B-cells since comparatively few plasma cells were found to be present. It is also possible, however, that the cells were of thymic origin but that they were unresponsive to phytohemagglutinin due to an active sensitization continuing against tumor-associated antigens. A less likely possibility is that the malignant cells inhibited the phytohemagglutinin response of the lymphocytes.

1631 ULTRASTRUCTURAL FEATURES OF CORTICOMEDULLARY CELLS IN A HUMAN ADRENOCORTICAL ADENOMA AND IN RAT ADRENAL CORTEX. (E.) Kovacs, K. (U. Toronto, Canada) and E. Horvath. *Anat Anz* 134(5):387-393, 1973.

A tumorous adrenal gland removed from a 15-yr-old boy with Conn's syndrome was studied ultrastructurally. Electron microscopy revealed the presence of corticomedullary cells in an aldosterone secreting adenoma arising from this gland. Similar cells were found in the temporarily ischemic adrenal cortices of three rats. Corticomedullary cells were absent in two adrenocortical adenomas associated with hypercorticism in human patients and in many adrenal glands of untreated rats. The corticomedullary cells do not appear to be regularly occurring constituents of either pathologic or normal adrenal cortical tissue. They are assumed to represent adrenocortical cells containing catecholamine granules squeezed into the cytoplasm: this might occur during removal, mincing, and fixation of the adrenal glands, or it may point up the ability of adrenocortical cells to take up catecholamine granules by some as yet unknown mechanism.

1632 GROSS AND ULTRASTRUCTURAL STUDIES IN A NEW MELANOMA MODEL: THE SINCLAIR SWINE.

(E.) Millikan, L. E. (U. Missouri Med. Ctr., Columbia), R. R. Hook and P. J. Manning. *Yale J Biol Med* 46(5):631-645, 1973.

A large number of melanocytic nevi characterize the Sinclair swine at their present stage of breeding. These tumors often dramatically regress in association with generalized depigmentation and occasionally evolve into diverse and metastasizing lesions. The melanocytes of these lesions and the clinical behavior of the tumors resemble the entire range of human melanocyte disorders from benign to malignant. The ultrastructural features of the porcine tumors closely resemble their human counterparts varying only in their melanin content (which is greater in the porcine tumors). Research into the etiology, progression, metastasis, and involution or therapy of melanocytic growth is now possible because of the close analogies demonstrated between this animal model and its human counterparts.

1633 CARCINOMA OF THE LUNG - A CORRELATIVE CYTOLOGICAL AND HISTOPATHOLOGICAL STUDY. (E.)

Garg, U. K. (S. N. Med. Coll., Agra, India), V. K. Srivastava, V. S. Rajvanshi and B. B. Maheshwari. *Indian J Cancer* 10(2):204-211, 1973.

Cytological and histological studies were performed using tissue biopsies, deep cough sputum, and bronchial washings from 82 cases of lung cancer. The results were examined for the relative incidence of different types of lung carcinoma as well as to assess the usefulness in cytological examination in diagnosis as compared to histological examination. Histologically, 46.3% of the cases involved epidermoid carcinoma, 28% involved small cell carcinoma, 20.7% involved adenocarcinoma, 2.4% involved alveolar carcinoma, and

4.8% involved large clear cell carcinoma. The results of the cytological examinations correlated closely with those from the histological examinations in 59 of the 82 cases studied (72%). However, in eight cases (10%), cytological examination yielded positive results while biopsy results were negative. In eight cases where bronchial biopsy was negative, histological proof of cancer was obtained. In summary, sputum cytology provided the diagnosis in 82% of the cases as compared to 83% of the cases diagnosed by histological examination. Epidermoid carcinoma and anaplastic carcinoma were diagnosed more frequently by cytological examination as compared to adenocarcinoma and large cell carcinoma. To obtain the maximal number of positive results, at least three repeat specimens of sputum should be examined cytologically.

- 1634 RNA-DIRECTED DNA-POLYMERASE ACTIVITY IN GREENE HAMSTER MELANOMA. (E.) Reid, T. W. (Yale U. Sch. Med., New Haven, Conn.), T. L. Darling, P. Russell and D. M. Albert. *Yale J Biol Med* 46(5):485-491, 1973.

Primary kinetic studies with RNA-directed DNA-polymerase from avian myeloblastosis virus indicated that this enzyme is stimulated by thymidine triphosphate (TTP). Similar results were obtained with pigmented and nonpigmented Greene hamster melanoma tumors. However, similar enzyme activity was not found in Greene hamster melanoma cells grown in tissue culture under normal conditions. Tissue culture cells treated with BUdR also showed little enzyme activity, although the pellet obtained by spinning the supernatant culture fluid at 100,000 g for 1 hr showed an increase in activity when the amount of TTP was increased. The activity required detergent (NP-40) and showed a preference for the synthetic RNA template over a DNA template. The activity is found with either Mg^{2+} or Mn^{2+} .

- 1635 LOW- AND HIGH-VOLTAGE ELECTRON MICROSCOPY OF A HUMAN NEUROBLASTOMA IN LONG-TERM ORGAN CULTURE. (E.) Lyser, K. M. (Inst. Exp. Embryol., Coll. France, Nogent-sur-Marne). *Cancer Res* 34(3):594-602, 1974.

- 1636 HISTOENZYMOLOGICAL CHARACTERISTICS OF SOME PROCESSES IN THE LUNG CONCOMITANT WITH BRONCHOPULMONARY CANCER. (Rus.) Kovalenko, V. L. (USSR Acad. Med. Sci., Moscow). *Vopr Onkol* 20(7):22-28, 1974.

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- 1638 EFFECT OF CYSTEINE ON THE SURVIVAL OF MICE WITH TRANSPLANTED MALIGNANT THYOMA. (E.) Campbell, N. R. (Dept. Dent. Med. Surg. U. Melbourne, Victoria, Australia), P. C. Reade and B. G. Radden. *Nature* 251(5471):158-159, 1974.

- 1639 GRADE 0 CERVICAL CARCINOMA: REPORT ON CLINICAL EXPERIENCE. (Ger.) Melzer, H. (Karl Marx Stadt Reg. Hosp., Germany), K. Schnabel, F. Genau and U. Wendel. *Zentralbl Gynaekol* 96(26):810-815, 1974.

- 1640 VERRUCOUS CARCINOMA OF THE VULVA. (Ger.) Buttner, H. H. (Clin. Obstet. Gynecol., U. Rostock, Germany) and H. Kyank. *Zentralbl Gynaekol* 96(26):816-818, 1974.

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- 1642 VERY SMALL MEGAKARYOCYTES IN CHRONIC MYELOID LEUKEMIA, ACUTE LEUKEMIA AND ERYTHRO-LEUKEMIA. (Ger.) Albrecht, M. (Moabit Munic. Hosp., Berlin, Germany) and H. H. Fulle. *Klin Wochenschr* 52(13):649-650, 1974.

- 1643 THE RESONANCE HYPOTHESIS OF CARCINOGENESIS: TRIPLET-TRIPLET RESONANCE ENERGY TRANSFER AS A CAUSE OF CELLULAR GROWTH REGULATION. (Ger.) Popp, F. A. (Radiol. Ctr., U. Marburg/Lahn, Germany). *Strahlentherapie* 146(5):583-589, 1973.

- 1644 CHROMOSOMAL HETEROGENEITY IN THE RAG AND MSWBS MOUSE TUMOR CELL LINES. (E.) Hashmi, S. (Coll. Phys. Surg., Columbia U., New York, N.Y.), P. W. Allderdice, G. Klein and O. J. Miller. *Cancer Res* 34(1):79-88, 1974.

- 1645 CHRONIC MEYLOGENOUS LEUKEMIA CELL GROWTH AND MATURATION IN LIQUID CULTURE. (E.) Golde, D. W. (U. California Ctr. Hlth. Sci., Los Angeles), L. A. Byers and M. J. Cline. *Cancer Res* 34(2):419-423, 1974.

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- 1650 ACETYLATED CORTICOTROPIN SUPPRESSION OF AGE INCREASE OF THE OVARIES WEIGHT IN MICE. (Rus.) Bulovskaya, L. N. (N. N. Petrov Res. Inst. Oncol., Leningrad, USSR), L. L. Maljugina and V. M. Diljman. *Vopr Onkol* 20(7):60-63, 1974.
- 1651 OSTEIOD OSTEOMA IN CHILDREN. (Rus.) Kovalenko, K. N. (Res. Inst. Surg. Tuberculosis, Leningrad, USSR), G. R. Bekzadyan and V. A. Talantov. *Vopr Onkol* 20(7):37-44, 1974.
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- 1653 FIBRINOLYTIC ACTIVITY OF BLOOD AND HEMATOGENOUS METASTASES SPREAD OF EXPERIMENTAL TUMORS. (Rus.) Sopotsinskaya, E. B. (Inst. Oncol. Problems, Acad. Sci., Kiev, USSR). *Vopr Onkol* 20(7):44-47, 1974.
- 1654 POLYADENYLATE-CONTAINING RNA OF POLYRIBOSOMES ISOLATED FROM RAT LIVER AND MORRIS HEPATOMA 7800. (E.) Tweedie, J. W. (U. Wisconsin Med. Sch., Madison) and H. C. Pitot. *Cancer Res* 34(1):109-114, 1974.
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- 1657 PHOSPHORYLATION OF ACID-SOLUBLE PROTEINS IN ISOLATED NUCLEOLI OF NOVIKOFF HEPATOMA ASCITES CELLS. EFFECTS OF DIVALENT CATIONS. (E.) Kang, Y.-J. (Baylor Coll. Med., Houston, Tex.), M. O. J. Olson and H. Busch. *J Biol Chem* 249(17):5580-5585, 1974.
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- 1664 ISOZYME VARIATIONS IN HUMAN MALIGNANT MELANOMA. (E.) Prasad, R. (Baylor Coll. Med., Houston, Tex.), M. M. Romsdahl, C. R. Shaw, D. M. Mumford and J. L. Smith, Jr. *Cancer Res* 34(6):1435-1438, 1974.
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GARSON, O.M. 1751*	GOH, E.H. 1444	GROSSMAN, M.R. 1663*
GATI, F. 1296	GOKCEN, M. 1386	GROVE, G.L. 1720*
GAVOSTO, F. 1592	GOLD, P. 1448	GROVER, P.L. 1242
GEDEON, F.M. 1721*	GOLD, S.B. 1551*	GRUNBERGER, D. 1268
GEHRING, D. 1625	GOLDE, D.W. 1645*	GRUNDER, G. 1473
GEHRING, P.J. 1295	GOLDEN, S. 1672*	GRUNKE-IOBAL, I. 1537*
GEHRKE, C.W. 1448	GOLDENBERG, D.M. 1447	GSCHWIND, C.R. 1472
GELBOIN, H.V. 1299	GOLDFARB, S. 1659*	GUERIN, C. 1777*
GELFANDBEIN, Y.A. 1610*, 1611*	GOLDIN, A. 1476	GULAK, D.V. 1412*
GEL'SHTEIN, V.I. 1586	GOLDMAN, L.I. 1482	GULLINO, M. 1248
GENAU, F. 1639*	GOOD, R.A. 1467	GUMAFER, K.I. 1253
GENCHEV, G. 1791*	GOODING, L.R. 1450	GUSEVA, L.N. 1383
GENES, I.S. 1781*	GOODMAN, H.M. 1429*	GUTMAN, H.R. 1282
GERARD, G.F. 1399	GOORHA, R. 1417*, 1426*	GUTTERMAN, J.U. 1472
GERFO, P.L. 1439	GORDIENKO, S.P. 1331*	GYLES, N.R. 1385
GERNER, R.E. 1358*	GORDON, H.H. 1434*	HACK, M.H. 1708*
GERSHENOVICH, Z.S. 1796*	GORSKI, J. 1771*	HACKNEY, J. 1292
GERSHON, R.K. 1498	GOURMELEN, M. 1627	HADDEN, J.W. 1517*
GERWIN, R.I. 1379	GOWING, N.F.C. 1548*	HADDOW, A. 1226*
GESER, A. 1581	GRABER, E.A. 1221	HADJIOLOFF, A.I. 1767*
GESER, A.G. 1582	GRAHAM, W.P., III 1353*	HADJIOLOV, D. 1240, 1244
GHANTA, V.K. 1613*	GRANBERG, P.-O. 1630	HADJIOLOVA, I. 1244
GILBERT	GRANOFF, A. 1417*, 1426*	HAGERSTRAND, I. 1474
1418*	GRANTHAM, P.H. 1310	HAGMAR, B. 1748*
GILBERT, H.S. 1713*	GRAW, J.J. 1230	HAIDER, S. 1433*
GILBERT, J. 1245	GREEN, M. 1399	HAINDAU, B. 1578
GILDEN, P. 1403	GREENWALD, P. 1530*	HAKOMORI, S.-I. 1519*
GILKERSON, E. 1737*	GREGORIADES, G. 1618*	HALLEY, J.B.W. 1479
GILMER, K.N. 1745*	GRIFFITHS, G. 1330*	HAMDY, F. 1421*
GIRAUDO CONESA, L.C. 1478	GRIFONI, V. 1211	HAMILTON, T. 1317*
GLAS, U. 1630	GRILLI, S. 1247	HAMLIN, N.M. 1613*
GLASEP, M. 1373		

HAMMARSTROM, S.	HIGHMAN, R.	HORVEN, I.
1442	1236	1619*
HAMMONS, A.S.	HILBORN, D.A.	HOSICK, H.L.
1276	1423*	1542, 1652*
HAN, T.	HILFRICH, J.	HOSOGI, Y.
1456	1232	1233
HANAUE, H.	HINO, S.	HOUGLUM, J.F.
1732*	1402, 1404	1681*
HANNA, M.G., JR.	HIRAI, H.	HSU, Y.-C.
1472	1529*	1541
HANSEN, H.J.	HIRAI, K.	HUANG, C.-C.
1447	1394	1776*
HARD, G.C.	HIRAMOTO, R.N.	HUMISTON, C.G.
1231	1613*	1295
HARDY, W.D., JR.	HIRANO, T.	HUNT, C.
1471	1339*	1584
HARRINGTON, J.S.	HIRAO, K.	HURVITZ, A.I.
1418*	1233, 1336*	1589
HARRIS, H.	HIRAYAMA, T.	IHAMAKI, T.
1508	1583	1615*
HASHIMOTO, Y.	HIROTA, T.	IMAGAWA, A.
1237	1552*	1233
HASHMI, S.	HITACHI, P.M.	IMAIZUMI, M.
1644*	1229	1685*
HATANAKA, M.	HOCKER, P.	IMASATO, K.
1403	1208	1724*
HAWKINS, R.P.	HOELZER, D.	IMMICH, H.
1444	1544	1346
HAWTHORNE, P.K.	HOERNER, G.V.	INBAR, M.
1704*	1590	1752*, 1756*
HAYAKAWA, M.	HOFFMANN, G.	INGLIS, P.J.
1523*	1625	1749*
HAYES, H.W., JR.	HOLREN, J.A.	INUYAMA, S.
1567	1376	1723*
HEADING, C.B.	HOLDEN, H.E., JR.	INUYAMA, Y.
1234	1661*	1723*
HEIDELBERGER, C.	HOLDER JUN, W.D.	IRVING, M.G.
1703*	1401	1479
HEIKKINEN, E.S.	HOLDORFF, B.	ISAKA, H.
1694*	1549*	1529*
HEIMPEL, H.	HOLLANDER, C.F.	ISHIGAMI, S.
1544	1564	1458
HEINIGER, H.-J.	HOLLINSHEAD, A.C.	ISHII, K.
1687*	1453	1583
HEJDA, V.	HOLM, G.	ISHIKAWA, A.
1558*	1442	1390
HELM, F.	HOLT, S.C.	ISHIKAWA, E.
1359*	1421*	1626
HELMICH, C.	HOLTZMAN, E.	ISHIKAWA, M.
1374	1516*	1741*
HELMY, F.M.	HOLUBAR, K.	ISHIMARU, T.
1708*	1359*	1342
HENRIKSEN, B.	HOOK, R.R.	ISHIZU, S.
1536*	1632	1318*
HERBERMAN, R.B.	HOPP, M.L.	ISOKOSKI, M.
1373, 1453, 1503	1203	1615*
HERBST, A.L.	HOPPENSTAND, R.D.	ITO, N.
1227*	1281	1233, 1336*
HERGENRADER, M.	HOPWOOD, J.J.	IVANOV, I.I.
1764*	1409*	1553*
HERSH, F.M.	HORIKAWA, M.	IVINS, J.C.
1472	1319*	1207
HEPVA, R.	HORREF, W.A.	IWA, N.
1694*	1717*	1435*
HERZ, F.	HORS, J.	IYIN, V.S.
1675*	1606*	1797*
HEUBNER, R.J.	HORVATH, E.	JACOBS, A.
1305	1631	1677*

JACOBS, N.J.	KASPRZAK, K.S.	KINNEAR, B.K.
1258	1273	1575
JAFFE, B.M.	KATAOKA, T.	KINOSHITA, H.
1217	1505	1723*
JAGELLA, H.P.	KATO, S.	KIRCH, M.F.
1438*	1435*, 1452	1492
JAMES, J.R.	KATO, T.	KIRCHNER, H.
1239	1793*	1373
JAMES, S.T.	KATZ, A.	KIRSTEN, W.H.
1258	1228*	1378
JAMPLIS, R.W.	KATZ, J.	KISLYAKOVA, N.D.
1676*	1672*	1782*
JANOWER, M.L.	KAUFMAN, H.	KISSMEYER-NEILSEN, F.
1345	1368	1477
JAROSLOW, B.N.	KAUL, A.	KITABATAKE, T.
1512	1344	1341
JARPLID, B.	KAWACHI, T.	KITAGAWA, H.
1800*	1552*	1314*
JENNINGS, A.W.	KAWAKAMI, S.	KJEPPE, K.E.
1759*	1678*	1477
JOLY, D.J.	KAWAKAMI, T.	KLEIN, F.
1595	1403	1359*, 1380, 1489
JONES, D.D.	KAZAN'EV, V.V.	KLEIN, G.
1730*	1742*	1411*, 1508, 1644*
JONES-WILLIAMS, W.	KEDAR, F.	KLEIN, K.L.
1528*	1484	1571
JORGENSEN, K.	KEEN, P.	KLEINFELDMAN, J.
1729*	1620*	1666*
JORI, A.	KFKKI, M.	KLEINFELD, M.
1304	1615*	1580
JOSWIG, N.	KELIN, E.	KLEMPNER, L.B.
1238	1473	1586
JUKARAINEN, E.	KELLEN, J.A.	KLUGE, N.
1694*	1249	1413*
KADIN, M.E.	KELLY, P.A.	KNIAZEFF, A.J.
1551*	1254	1281
KADING, J.	KEMMER, W.	KNOWLES, M.D.
1774*	1351	1245
KAISER, N.	KEMMERLE, M.	KOBAYASHI, H.
1700*	1290	1365, 1655*
KAISERLING, E.	KENDRICK, J.	KOCHRA, R.J.
1525*	1276	1295
KALISS, N.	KEOGH, M.D.	KODA, T.
1465	1530*	1458
KAMATA, Y.	KERSEY, J.H.	KODAMA, T.
1709*	1467	1365, 1655*
KAMATAKI, T.	KESSLER, I.I.	KOESTERER, R.
1314*	1569	1512
KANAI, K.	KEYL, A.C.	KOGA, S.
1502	1337*	1341
KANASUGI, K.	KFYS, A.	KOGAN, I.YA.
1552*	1598	1412*
KANG, Y.-J.	KHOO, S.K.	KOGURE, K.
1657*	1443, 1445, 1509	1552*
KANI, T.	KIEFER, G.	KOHLER, P.O.
1233	1288	1771*
KANISAWA, M.	KIEFFER, R.	KOHN, R.R.
1291	1288	1499
KANNEL, W.B.	KIHARA, T.	KOHNE, D.
1598	1325*	1403
KAPADIA, G.J.	KIMELBERG, H.K.	KOIKE, N.
1259	1292	1724*
KAPLAN, A.R.	KIMURA, I.	KOLOMIYETS, O.L.
1667*	1431*	1383
KAPLAN, B.L.	KIMURA, M.	KOMITOWSKI, D.
1610*, 1611*	1709*	1382
KARCHMER, R.K.	KING, J.P.G.	KONDO, K.
1357*	1518*	1724*

KOPROWSKI, H. 1388	LARSEN, S.O. 1572	LITMAN, A. 1735*
KOSS, L.G. 1215, 1675*	LASNE, C. 1284	LIU, P.I. 1342
KOVACS, K. 1631	LAVIALLE, C. 1395	LLOYD, A.G. 1234, 1316*
KOVALENKO, K.N. 1651*	LAVRIN, D.H. 1373	LO GERFO, P. 1463
KOVALENKO, V.L. 1636*	LAYARD, M. 1339*	LO, K.W. 1688*
KOWATSCHE, J. 1658*	LEDUC, F.H. 1661*	LOBENWEIN-WEINEGG, E. 1513*
KOYAMA, Y. 1552*	LEE, C.W. 1259	LONGMIRE, W.P., JR. 1695*
KOZLOV, JU.P. 1412*	LEE, D.J. 1257, 1337*	LONGNECKER, D.S. 1258
KREMENTZ, E.T. 1575	LEHMEYER, J.E. 1747*	LORENZ, D. 1348
KRICHEVSKAYA, A.A. 1796*	LEHTOLA, J. 1615*	LOTLIKAR, P.D. 1328*
KRIPIKE, M.L. 1213	LEIGH, J.S., JR. 1692*	LOVE, R. 1321*
KRUGER, F.W. 1232, 1235	LEONARD, J.C. 1518*	LOWE, R.F. 1608*
KRUGER, G.R.F. 1209	LETEXIER, A. 1606*	LUCARELLI, G. 1731*
KRUPEY, J. 1448	LEVENBOK, I.S. 1383	LUCAS, F.V. 1671*
KRUSCH, A.J. 1563	LEVIN, S.G. 1340	LUKAS, R. 1370
KULCAR, Z. 1569	LEVINE, P.H. 1360	LUNTOVSKAYA, V.A. 1782*
KURIHARA, T. 1678*	LEVINSON, W.E. 1429*	LUTZNER, M.A. 1248
KUROBANE, T. 1740*	LEVY, A.H. 1483	LYNCH, H.T. 1563, 1667*
KURODA, K. 1291	LEVY, L.S. 1255	LYNCH, J.F. 1667*
KUZUMAKI, N. 1365	LEWIS, B.J. 1391	LYON, J.L. 1616*
KYANK, H. 1640*	LEZHNEVA, O.M. 1521*	LYSER, K.M. 1635*
KYLE, W.E. 1663*	LIBERTI, P. 1533*	LYTEL, C.D. 1369
LAFEVERGES, F. 1296	LIKHTE, V.V. 1495	MACH, J.-P. 1459
LAGIOS, M.D. 1760*	LILIFELD, A.M. 1593, 1595	MACHIDA, K. 1741*
LAING, W.N. 1222*	LILLINGTON, G.A. 1676*	MACKAY, B. 1670*
LAKF, B.G. 1234	LIN, T.-Y. 1531*	MACKAY, E.V. 1443, 1445, 1509
LAMBERT, R. 1609*	LIN, W.-S.-J. 1531*	MACLEOD, R.M. 1747*
LAMM, L.U. 1477	LINDERBERG, L.G. 1437*	MADSEN, N.P. 1307
LAMON, E.W. 1489	LINDER, G.T. 1546	MAEROVICH, I.M. 1610*, 1611*
LANDERS, M.K. 1337*	LINDSAY, J.W. 1425*	MAGEE, P.N. 1202
LANDON, J. 1769*	LINDSTEN, J. 1798*	MAHESHWARI, B.B. 1633
LANDRUM, S. 1787*	LINDSTROM, C. 1547	MAIE, O. 1793*
LANGEZAAL, O.A.M. 1722*	LIOTTA, L.A. 1666*	MAK, I. 1428*
LAPIN, V. 1532*	LIPPIN, A. 1507	MAK, S. 1428*

MAKIURA, S. 1336*	MCCOLLISTER, S.B. 1295	MILLER, S.J. 1274
MALICK, L.F. 1661*	MCGRFGOP, D.H. 1342	MILLER, W.R. 1317*
MALING, H.M. 1236	MCGUIRE, W.L. 1707*, 1759*, 1772*	MILLIGAN, W.J. 1751*
MALJUGINA, L.L. 1650*	MCWFENY, D.J. 1245	MILLIKAN, L.E. 1632
MANDYBUR, T.I. 1560*	MEGN, J.L. 1327*	MIMS, C.H. 1559*
MANNICK, J.A. 1495	MEIER, H. 1305	MINAMI, M. 1318*
MANNING, P.J. 1632	MEITES, J. 1254	MINGEOT, R. 1303
MANSSON, P.E. 1762*	MELAMED, M.P. 1763*	MINOP, P.D. 1788*
MARQUARDT, H. 1242	MELDERIS, H. 1413*	MIRAND, F.A. 1364
MARSH, J.L. 1695*	MELLSTEDT, H. 1442	MIRONESCU, S. 1321*
MARSTON, S.D. 1490	MELNICK, J.L. 1493	MIRZOYAN, E.E. 1785*
MART, H. 1340	MELZER, H. 1639*	MITCHELL, D.N. 1441
MARTELLI, A.B. 1728*	MENCONI, E. 1476	MITCHELL, M.S. 1498
MARTIN, A.P. 1671*	MENNEL, H.D. 1324*	MITCHELL, R.B. 1720*
MARTIN, D.H. 1285	MENON, M. 1512	MITCHEN, J.R. 1718*
MARTIN, D.S. 1679*	MENZOIAN, J.O. 1496	MITELMAN, F. 1387
MARX, J.L. 1220	MERCURI, O. 1739*	MIYAKI, K. 1291
MASEK, M.A. 1787*	MEREKALOVA, Z.I. 1427*	MIYAZI, T. 1347
MASON, T.J. 1568, 1602	MERENDA, C. 1459	MODAN, G. 1340
MASUR, S.K. 1515*	MERINO, F. 1481	MOGENSEN, B. 1477
MATIDLI, G. 1362	MERLETTI, L. 1430*	MOHAN, L.C. 1310
MATSUMOTO, K. 1709*	MERRILL, A.H., JR. 1261	MOHR, U. 1235
MATSUMURA, K. 1233	MESSITE, J. 1580	MOKYR, M.B. 1498
MATSUSHITA, K. 1723*	MEUNIER, M. 1308	MONATOVA, T.I. 1785*
MATTERN, C.F.T. 1379	MEURET, G. 1625	MONKMAN, G.R. 1207
MATTHEWS, H.R. 1749*	MEURMAN, L.O. 1579	MOORE, D.H. 1376
MATTINGLY, R.F. 1545	MEYER, C.A. 1389	MOORE, G.E. 1358*, 1718*
MAUGH, T.H., II 1224*	MICHEL, G. 1511	MOORE, J.O. 1571
MAVLIGIT, G. 1472	MIKO, M. 1692*	MOORE, W.M., III 1779*
MAYHEW, E. 1292	MILLER, C.O. 1789*	MORA, P.T. 1446
MAZET, G. 1744*	MILLER, H. 1299	MORAN, E.M. 1706*
MAZURENKO, N.P. 1427*	MILLER, J.M. 1702*	MORGAN, D.L. 1248
MCBRIDE, A. 1624*	MILLER, O.J. 1644*	MORGAN, H.R. 1494
MCCOLLISTER, D.D. 1295	MILLER, R.W. 1646*	MORGAN, R.W. 1591

MORI, M.	NAGY, S.U.	NOVAK, D.
1266	1329*	1499
MORI, T.	NAITON, M.	NOZUE, Y.
1347, 1352	1452	1347
MORIN, M.	NAKAJIMA, T.	NUKADA, T.
1606*	1732*	1685*
MORIWAKI, S.	NAKAMURA, K.	OBENRADER, M.
1725*	1583	1754*
MORRIS, H.P.	NAKAMURA, R.M.	OBOSHI, S.
1663*, 1671*, 1681*, 1688*	1505	1404
MORROW, J.	NAKATSU, S.L.	ODA, T.
1660*	1787*	1502
MORSE, N.	NAKAYAMA, K.	OETTGEN, H.F.
1763*	1724*	1212
MORSON, B.	NANDI, S.	O'GARA, R.W.
1561*	1374, 1375, 1542	1259
MORTENSEN, R.F.	NAVRATILOVA, A.	OKABE, H.
1363	1515*	1403
MORTON, J.F.	NAZERIAN, K.	OKADA, F.
1259, 1335*	1380	1685*
MOSDAL, J.R.	NEGREI, L.N.	OKADA, M.
1522*	1312	1237
MOSER, K.	NELSON, R.L.	OKAMOTO, T.
1208	1629	1352
MOSFS, H.L.	NELSON-REES, W.A.	OKANZIMA, H.
1400	1704*	1352
MOTT, G.E.	NERY, R.	OLIER, C.
1659*	1449	1794*
MOULTON, A.	NETTESHEIM, P.	OLIN, T.
1439	1276	1436*
MOURALI, N.	NEUMANN, H.	OLINICI, C.D.
1590	1706*	1250
MOYKE, M.	NEURATH, A.P.	OLIVA, H.A.
1535*	1507	1554*
MULCAHY, G.M.	NEVILLE, A.M.	OLSON, M.O.J.
1563	1449	1657*
MULLER, B.	NEWCOM, S.R.	OMENN, G.S.
1344	1551*	1705*
MUMFORD, D.M.	NEWCOMB, E.W.	OPPENHEIM, W.
1664*	1461	1520*
MUNDT, D.	NEWELL, G.R.	ORTIZ DE LANDAZURI, M.
1240	1575	1484
MUNJAL, D.	NIELSEN, H.	ORWOLL, G.
1497	1556*	1207
MURRAY, B.K.	NIELSEN, M.	OSBORN, J.E.
1366	1556*	1392
MURRAY, P.R.	NIKILIN, A.A.	OSKIVIG, R.
1408*	1649*	1455
MUSCATO, J.J.	NIMBERG, R.B.	OSSOWSKI, L.
1688*	1496	1393, 1405
MUTH, H.	NISHIMURA, H.	OSTERTAG, W.
1351	1325*	1413*
MYERS, M.	NOGALES, F.F., JR.	OVE, P.
1737*	1554*	1754*
MYERS, M.W.	NOMURA, T.	OYASU, R.
1684*	1287	1203
MYGIND, N.	NORDEN, A.	OZER, H.L.
1536*	1762*	1390
MYKING, A.O.	NORDQUIST, R.E.	PADGETT, B.L.
1414*, 1415*	1705*	1392
MYLLARJEMI, H.	NORGAARD-PEDERSEN, B.	PAI, S.R.
1697*	1457	1539
NABEMBEZI, J.S.	NORMAN, K.K.	PALMIERI, G.M.A.
1601	1797*	1705*
NAGASAWA, H.	NORRIS, J.S.	PANCAKE, S.J.
1302	1771*	1446
NAGEL, D.	NORTHAM, B.E.	PANEM, S.
1275	1518*	1378

PANKOV, A.K. 1782*	PINGGERA, W.F. 1513*	QIZILBASH, A.H. 1355*
PAPAGEORGE, A.G. 1379	PITOT, H.C. 1654*, 1659*	QUEISSER, U. 1544
PAPAS, T.S. 1419*	PITTERMANN, E. 1208	QUEISSER, W. 1544
PARAF, A. 1746*, 1777*	PLUZNIK, D.H. 1735*	QUIGLEY, J.P. 1393, 1405
PARKER, J.E. 1570	POHL, R.J. 1294	RADDEN, B.G. 1638*
PARKS, L.C. 1462	POLAN, A. 1530*	RAGAB, A.H. 1737*
PARKS, W. 1403	POLLARD, M. 1454	RAICK, A.N. 1298
PARRY, D.H. 1677*	POPESCU, N.C. 1629	RAINER, H. 1208
PARSONS, J.A. 1758*	POPOVA, G.N. 1778*	RAJRHANDARDY, U.L. 1719*
PARUNGO, F.P. 1350	POPP, E.A. 1643*	RAJVANSHI, V.S. 1633
PASTERNAK, G. 1210	PORCELLINI, A. 1731*	RAM, M.D. 1499
PATTERSON, J.B. 1206	POROSHIN, K.K. 1637*	RAN, K.V. 1539
PATTERSON, L.T. 1385	PORTER, D. 1764*	RAPP, H.J. 1299
PAUL, J. 1757*	PORTER, K.R. 1665*	RASCHKE, W.C. 1451
PAUL, D. 1598	POSNER, M. 1768*	RATCLIFFE, J.G. 1769*
PAVELIC, Z. 1736*	POTTER, E.V. 1524*	RAUSCH, R.L. 1425*
PAVLOVSKY, A. 1478	POTVIN, C. 1485	RAWLS, W.E. 1483, 1569
PAYNE, P.M. 1584	POUP, P. 1235	RAY, B. 1799*
PAZMINO, N.H. 1487	POURREAU-SCHNEIDER, N. 1470	RAY, P. 1332*
PECKHAM, J.C. 1628	POVSLEN, C.O. 1506	READ, P.C. 1638*
PEEBLES, P.T. 1379	PRADHAN, S.N. 1332*	REDDY, D.V.R. 1431*
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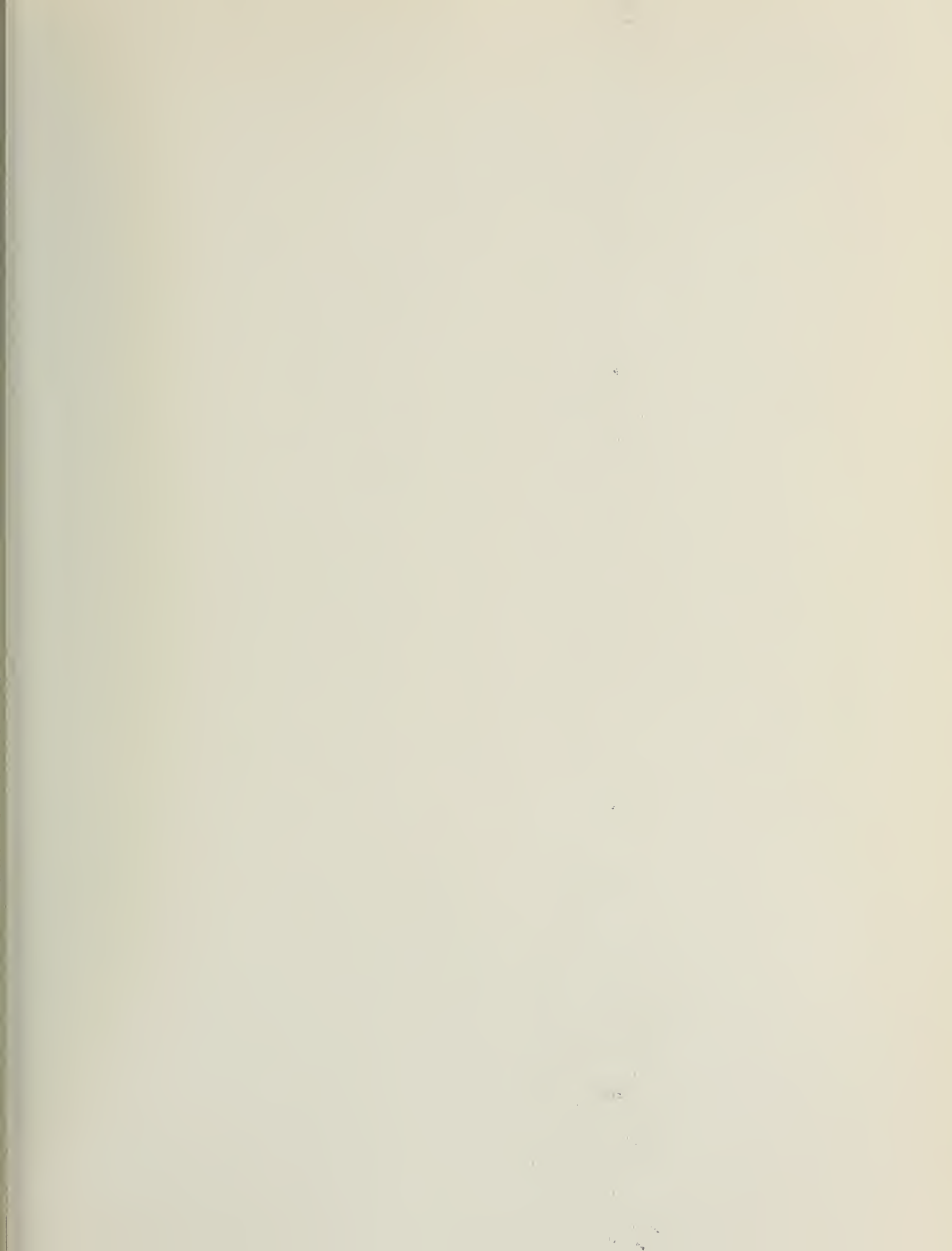
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N O T I C E

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PREFACE

Carcinogenesis Abstracts is a publication of the National Cancer Institute. The journal serves as a vehicle through which current documentation of carcinogenesis research highlights are compiled, condensed, and disseminated on a regular basis. It represents an integral part of the Institute's program of fostering and supporting coordinated research into cancer etiology. Issues of *Carcinogenesis Abstracts* normally contain three-hundred abstracts and three-hundred citations (unaccompanied by corresponding abstracts). Abstracts and citations refer to the current scientific literature that describes the most significant carcinogenesis research carried on at the National Cancer Institute, other governmental agencies, and private institutions. *Carcinogenesis Abstracts* is intended to be a highly useful current awareness tool for scientists engaged in carcinogenesis research or related areas. The great number and diversity of publications relevant to carcinogenesis make imperative the availability of this service to investigators whose work requires that they keep abreast with current developments in the field.

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
ln.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	RNA	ribonucleic acid
i.m.	intramuscular	s.c.	subcutaneous
i.p.	intraperitoneal	sec	second(s)
IU	international unit(s)	U	unit(s)
i.v.	intravenous	UV	ultraviolet
kg	kilogram(s)	WBC	white blood cells (leukocytes), white blood count
LD ₅₀	median lethal dose(s)	wk	week(s)
m	meter(s)	wt	weight(s)
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
µM	micromolar		
mC, µC	milli-,microcurie(s)		

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- 1801 VIRUSES AS IMMUNOLOGICAL ADJUVANTS IN CANCER. (E.) Lindenmann, J. (Inst. Med. Microbiol., U. Zurich, Switzerland). *Biochim Biophys Acta* 355(1):49-75, 1974.

Homogenates of tumor cells infected with certain viruses are more immunogenic than similar extracts from noninfected cells. This phenomenon has been most thoroughly studied with nonspecific tumors and influenza virus, but it has also been demonstrated using strain-specific tumors and other viruses. A hypothesis is offered according to which associations of the carrier-hapten type occur at several levels during viral growth. The necessity of working with fully adapted viruses is stressed. Viruses which seem suitable for the purpose of "virus-assisted immunotherapy" in man have been adapted to human malignant tissues, and a research strategy towards human applications is proposed. (138 references)

- 1802 CONTROL OF CELL PROLIFERATION AND DIFFERENTIATION IN THE NORMAL STOMACH. (E.) Willems, G. (St. Pierre Hosp., Brussels, Belgium). *Rev Gastroenterol* 5(3):196-203, 1973.

During the last decade a basic pathophysiological interest in the gastric kinetic processes led several investigators to intensify research in this field, resulting in significant advances in the understanding of the normal control factors of cell proliferation and differentiation in the stomach. This review provides a survey of the current knowledge on this subject in the light of recent experimental work, including nyctohemeral variations, the effects of fasting and refeeding, the effect of gastrin, and vagal effects. (54 references)

- 1803 POSSIBLE PRINCIPLES FOR STANDARDIZING CARCINOGENS. (Rus.) Dikun, P. P. (N. N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR). *Gig Sanit* (2):91-95, 1974.

An attempt is made to resolve the long-standing dispute between hygienists and oncologists about the possibility of establishing the maximum permissible doses (MPD) and maximum permissible concentrations (MPC) of chemical carcinogens discharged into the environment. Attempts are currently being made to establish MPD and MPC for polycyclic aromatic hydrocarbons (PAH), particularly for 3,4-benzpyrene released into the air and water. A more promising approach may involve the technological standardization of carcinogenic discharge sources. It is frequently possible to set very low carcinogenic discharge standards, avoiding costly modification of technological processes. Observance of the standards will merely require proper operational procedures and equipment maintenance. On the other hand, some of the currently employed technologies release large amounts of carcinogenic PAH, particularly into smoked foods. Essential changes must first be made in the production technology with new discharge standards to follow. (6 references)

- 1804 THE BREAKAGE-AND-REUNION THEORY AND THE EXCHANGE THEORY FOR CHROMOSOMAL ABERRATIONS INDUCED BY IONIZING RADIATIONS: A SHORT HISTORY. (E.) Revell, S. H. (Inst. Cancer Res., Belmont, Surrey, England). *Advances in Radiation Biology*, New York, Academic Press, 1974, pp. 367-416.

This review attempts to evaluate present theories on how to interpret the changes in chromosome structure seen at mitosis after cells have been exposed to ionizing radiations. The review intends to be a guide to the mechanics of chromosomal aberrations. It first describes the different forms of aberration as these appear at the first mitosis after radiation treatment. Then it describes the two opposing theories, that is breakage-and-reunion and exchange, and the experimental evidence from which they arose. The implications of the two theories are compared. Various questions and misunderstandings concerning them are dealt with, as is recent work undertaken with the purpose of testing the different predictions of the two theories. In conclusion, the author presents different experimental approaches to this problem. (74 references)

- 1805 LYSOSOMES IN CANCER CELLS. (E.) Allison, A. C. (Clin. Res. Ctr., Harrow, England). *J Clin Pathol [Suppl]* 27(7):43-50, 1974.

The role of lysosomes in tumor cells is outlined. Lysosomal enzyme activities are often higher in tumors than in the corresponding normal cells. This is related in part to the undifferentiated state of the tumor cells. Similarly, relatively high proportions of lysosomal hydrolases not sedimentable with cytoplasmic particles are often found in tumors. This is related in part to the presence of autophagosomes, which are easily disrupted by homogenization, and in part to autolysis. Release of hydrolases from tumor cells may facilitate the penetration of normal tissues and the detachment from tumors of cells which can metastasize. Regression of hormone-dependent tumors is an endocidal event in which autophagosomal digestion plays an important part. The formation of autophagosomes and other lysosomal changes frequently occur during cancer therapy. Proteases, probably acting on membrane glycoproteins, can release cells from growth control. (71 references)

- 1806 INDUCTION OF LIVER GROWTH BY XENOBIOTIC COMPOUNDS AND OTHER STIMULI. (E.) Schulte-Hermann, R. (Inst. Toxicol. Pharmacol., Phillips U., Marburg, W. Germany). *Critical Reviews in Toxicology (Cleveland)* 3(1):97-158, 1974.

Literature pertaining to the induction of "additive" liver growth (i.e., the growth exceeding characteristic adult proportions) by xenobiotic compounds is reviewed. Many drugs, including hypnotics, sedatives, anesthetics, CNS stimulants, antipsychotics, tranquilizers, antihistamines, anti-inflammatory agents, hypolipidemic drugs, fungicides and sympathomimetics, have been found to induce liver growth usually ranging from 10-50%. The capacity to induce liver en-

largement depends, in general, on the rate of metabolism of the drug. Most inducers are substrates of hepatic microsomal drug-metabolizing enzymes and can stimulate activity of these enzymes. Most of the agents possess a nonpolar region which permits lipid solubility at physiologic pH and thus may induce liver growth. Liver enlargement is usually secondary to an increase in parenchymal mass, with hypertrophy and hyperplasia contributing to varying degrees. Activation of the genetic apparatus of the liver cell is probably involved in the growth response, but the initial events of the inductive process are unknown. Although the enlarged livers usually show no pathologic changes, adverse effects may possibly result from increased mixed-function oxidase activities and from altered sensitivities toward hepatotoxins or carcinogens. (550 references)

- 1807 USE OF VIRUSES FOR MEASURING THE TRANSFER OF HETEROGENEOUS FUNCTIONAL DNA FROM CELL TO CELL. (Fr.) Melnick, J. L. (Baylor Coll. Med., Houston, Tex.), A. L. Boyd and J. S. Butel. *Bull Inst Pasteur (Paris)* 71(4):397-427, 1973.

Three studies are discussed in which the method of DNA transfer was applied in order to introduce foreign DNA from mammalian cells into receptive heterologous cells. The first study on recovery of SV40 virus from transformed cells includes: (1) a review of the literature on general properties of SV40 transformed cells, including viral nucleic acids in transformed cells, viral antigens in transformed cells, and recovery of the transforming viral genome; (2) a general method for recovering the virus with the aid of "DNA transfer" and a method for obtaining SV40 from productive and nonproductive cell lines; and (3) the significance and four hypotheses for the mechanism by which integration of the viral genome is maintained. The second study deals with modifications occurring in hamster cells after incubation with DNA from simian cells. The choice of a system and adsorption of poliovirus by DNA-treated hamster cells are considered. This study demonstrated the possibility of transferring a functional DNA from simian cells to hamster cells in the presence of DEAE-dextran. The third study, formation of heterologous SV40 pseudovirus, includes a description of pseudovirions and incorporation of DNA from hamster cells into SV40 particles. Pseudovirion "sub-products" of a normal viral replicative cycle resemble the bacteriophage of "generalized transduction." Exogenous DNA may be encapsulated in SV40 particles, showing that the production and detection of heterologous pseudovirions may be possible. No biological activity has yet been demonstrated for heterologous pseudovirions. The method of DNA transfer is considered promising for passage of genetic information between mammalian cells. However, the usefulness of this method for transmission of genetic information between somatic cells is probably limited by a technical inability to locate numerous genetic markers in such systems. It is too early to form hypotheses concerning the relative merits of the 3 general approaches described and to attempt to predict which will ultimately be most useful. (83 references)

- 1808 CELL SURFACES IN NEOPLASIA. (E.) Easty, G. C. (Inst. Cancer Res., London, England). *Neoplasia and Cell Differentiation*, Basel, Karger, 1974, pp. 189-233.

The association between the abnormal growth and behavior of neoplastic cells and alterations in the surfaces of these cells relative to their normal counterparts is reviewed. The composition of the plasma membrane-surface complex is considered in terms of its chemical composition and the problems associated with its isolation, while its structure is considered with regard to the bimolecular lipid layer model and the globular micelle model. The lipid, carbohydrate, sialic acid, and ionogenic composition of the plasma membrane complexes of normal and malignant cells is also discussed, as are tumor specific antigens, embryonic antigens, and the loss of antigens from the cell surface. Consideration is also given the structural and chemical basis for the reduced cell-cell adhesiveness of malignant cells, and cell contacts and the formation of metastases. The contact regulation of normal and malignant cells is discussed in terms of the contact inhibition of movement *in vitro*, the functional junctions between cells, contact inhibition of cell proliferation, and metabolic cooperation between cells in contact. The review concludes with a discussion on the formation of metastases and cell contacts. (268 references)

- 1809 EFFECT OF AFLATOXINS ON ANIMAL CELLS IN TISSUE CULTURE. LITERATURE REVIEW. (Rus.) Beniumovich, M. S. (Inst. Nutr., Moscow, USSR). *Farmakol Toksikol* 36(4):497-501, 1973.

Literature on the following aspects of the use of tissue culture for the study of properties of aflatoxins is reviewed: (1) production of aflatoxin preparations and method of introducing them into cultures; (2) characteristics of cultures used to study the effects of aflatoxins; (3) toxicity of aflatoxins in tissue culture; (4) characteristics of changes caused by aflatoxins in cultured cells and mechanisms of aflatoxin action; (5) specificity of the toxic effect of aflatoxins in cell cultures, and (6) comparison of data obtained *in vivo* and in tissue culture. Experiments with cell and tissue culture indicate high sensitivity to the effect of aflatoxins in populations of rapidly propagating cells, although the sensitivity of cells of various stable lines varies to a known degree. Aflatoxin-induced damage occurs primarily in cells undergoing mitosis. Hepatocytes are apparently more sensitive to aflatoxins *in vitro* than cultured cells of other organs. However, under conditions of retarded propagation (primary trypsinized cultures, diploid lines) the resistance of hepatocytes and their derivatives to aflatoxins is probably quite high. The *in vitro* effect of aflatoxins on nonpropagating liver cells requires further study. Research on the use of tissue culture methods for study of the selective sensitivity of liver cells to aflatoxins is of considerable interest. Aflatoxins are not known to have a carcinogenic effect on cultured cells. (22 references)

1810 NON-EPITHELIAL TUMORS OF THE NASAL CAVITY, PARANASAL SINUSES, AND NASOPHARYNX: A CLINICOPATHOLOGIC STUDY. III. CARTILAGINOUS TUMORS (CHONDROMA, CHONDROSARCOMA). (E.) Fu, Y.-S. (Med. Coll. Virginia, Richmond) and K. H. Perzin. *Cancer* 34:453-463, 1974.

In a review of cartilaginous (chondroma and chondrosarcoma) tumors involving the nasal cavity, paranasal sinuses, and nasopharynx, 256 lesions, 156 benign and 100 malignant, were identified. Of these, 17 were cartilaginous neoplasms, seven chondromas and ten chondrosarcomas. The clinical findings associated with these cartilaginous tumors are described, the histologic features illustrated, results of therapy presented, and clinicopathologic correlations made. Chondromas were small asymptomatic incidentally found nodules which were successfully treated by limited local resections and were without recurrence. The prognosis of the chondrosarcomas depended upon: 1) the location and extent of the lesion; 2) the adequacy of the surgical therapy for resectable tumors; and 3) the degree of differentiation of the tumor. (24 references)

1811 PRIMARY MALIGNANT MELANOMA OF THE ORAL CAVITY IN JAPAN. (E.) Takagi, M. (Tokyo Med. Dental U., Japan), G. Ishikawa and W. Mori. *Cancer* 34:358-370, 1974.

This paper is a review of 120 cases of primary malignant melanoma of the oral cavity occurring in the Japanese. Since malignant melanoma and ectopic pigmentation are relatively common in Japan, an assumption has grown as to a possible relationship to histogenesis. The analysis of the material and the discussion are focused on these points. Some of the cases do not seem to have any relation to oral melanosis, but almost two-thirds of the cases were found associated with it (36.2% of melanoma was associated with preexisting melanosis, and 29.8% with concurrent or later-developing melanosis). The biological behavior and histologic patterns of these melanoses were similar to those of lentigo maligna of the skin. The preexisting melanoses seemed to be the most common precancerous lesion of the oral mucosa as far as malignant melanoma was concerned. (36 references)

1812 MULTIPLE TUMORS OF THE SKIN: CLINICAL, HISTOPATHOLOGICAL, AND GENETIC FEATURES. (E.) Berendes, U. (U. Clin. Heidelberg, W. Germany). *Humangenetik* 22(3):181-210, 1974.

The clinical features, histopathology, and genetic data of multiple lipomata, steatocystoma multiplex, multiple cutaneous leiomyomata, multiple glomus tumors, and blue rubberbleb nevus syndrome are reviewed and summarized. The hypothesis of autosomal-dominant inheritance in these tumors of the skin is statistically examined by means of the maximum-likelihood procedure. This hypothesis could be confirmed for multiple lipomata, steatocystoma multiplex, and is very probable in the case of multiple leiomyomata

and multiple glomus tumors. Data on blue rubberbleb nevus syndrome are not sufficient to give a definite judgement. Available information suggests dominance with almost complete penetrance of the gene. The fact is stressed that solitary and multiple skin tumors are two basically different entities. The underlying mutational events in the multiple variant are discussed and problems involving frequency, manifestation, and clinical variability of the disorders are presented. (147 references)

1813 TOBACCO SMOKING AND LUNG CANCER. (Rus.) Serebrov, A. I. (No affiliation). *Sov Med* (7):109-112, 1973.

There is indisputable evidence that smoking is largely responsible for lung cancer. The lung cancer mortality rate is 20 times higher among smokers than among nonsmokers. The incidence of angina pectoris is 13 times higher among smokers, that of myocardial infarction, 12 times higher, and that of stomach ulcer, 10 times higher than among nonsmokers. The temperature in the cigarette end during inhalation reaches 700°C, resulting in the formation of benzpyrene, a carcinogenic agent. Morphological studies of 117 patients who died of lung cancer show carcinoma *in situ* in 1% of non-smokers autopsied, in 4.1% in lungs of males who smoked less than one pack of cigarettes a day, and in 6% of men who smoked more than one pack. Combatting the smoking habit is frustrated by tobacco and cigarette manufacturers. Measures to combat smoking must include large-scale campaigns against smoking, restriction of advertising, inclusion of anti-smoking warnings in all packs, recommendations of health-conscious smoking technique and a variety of other social and economic measures. The lung cancer mortality rate among those who give up smoking drops to 1/20 within three years after giving up the habit. (No references)

1814 CASE CLUSTERING IN HODGKIN'S DISEASE: A BRIEF REVIEW OF THE PRESENT POSITION AND REPORT OF CURRENT WORK IN OXFORD. (E.) Smith, P. G. (Dept. Hlth. Soc. Security, Oxford U., England) and M. C. Pike. *Cancer Res* 34(5):1156-1160, 1974.

The most important investigation of possible case clustering of Hodgkin's disease (HD) to date was that of Vianna *et al* in Albany County, New York. Assuming that the Albany situation was not simply a chance occurrence, this data must be used to determine whether HD patients are infective before and/or after diagnosis. It is not yet obvious that transmission was taking place. Space-time distribution studies are unlikely to be a useful means of continuing investigation into HD in view of its probably long and variable latent period. Two studies have been undertaken to test the Albany findings. A case-control study of contacts is making use of a matched control group selected from patients not suffering from a chronic or malignant disease admitted to hospitals in the same year as the HD patients. Preliminary results do not indicate that

the HD patients had more contact with each other prior to diagnosis of the disease than did controls. A study of the transmission of HD in schools was set up to test the hypothesis that the amount and type of contact that occurs between school students and between school students and their teachers is favorable for transmission. Attempts are being made to link teachers and young persons with HD to each other and to do the same with a control group. (10 references)

- 1815 NEW VINYL CHLORIDE-EXPOSURE REGS DRAW FIRE. (E.) Anonymous. *Oil Gas J* 72(40):52, 1974.

Industry reaction to the Labor Department's new vinyl chloride exposure regulation, which sets levels of 1 ppm averaged over an 8-hr period, are summarized. It will become mandatory for workers exposed to more than the 1 or 5 ppm (for any 15-min period within the 8-hr time span) levels to wear respirators. Industry questions its ability to meet the level of 1 ppm in the time specified and is seeking remedies through the judicial process. The standard also calls for regular monitoring of plant air, regular medical examinations for workers, and the setting up of regulated areas where vinyl chloride exposure is high.

- 1816 THE CARCINOGENIC PROPERTIES OF VINYL CHLORIDE. (Dut.) 'de Engelse, L. (Netherlands Cancer Inst., Amsterdam) and P. Emmelot. *Chem Weekblad* 70(28/29):5;7-8, 1974.

Recent studies on the carcinogenicity of vinyl chloride and related legislation are reviewed in the light of the significantly increased incidence of angiosarcoma of the liver in workers exposed to this compound in the air of polyvinylchloride (PVC) plants. A total of 19 cases of angiosarcoma of the liver have thus far been detected in workers exposed to vinyl chloride. Angiosarcoma of the liver and other tumors developed in rats and mice exposed to 250 and 50 ppm concentrations of vinyl chloride for 4 hr/day, 5 days/wk, for several months. These findings have prompted a reduction of the maximum permissible concentration to 50 ppm, but a further reduction of this limit appears necessary. Extensive epidemiological surveys on the incidence of liver injury and liver tumors among active and retired workers in PVC manufacturing plants, and experiments on the carcinogenicity of vinyl chloride at concentrations lower than 50 ppm are being conducted. (5 references)

- 1817 CONTRIBUTION OF GENERAL ONCOLOGY TO THE UNDERSTANDING OF LUNG CANCER. (Fr.) Israel, L. (Lariboisière U. Hosp. Ctr., Paris, France). *Rev Prat* 23(13):1147-1155, 1973.

The notion of orderly growth of cancers comes from general and experimental oncology. The mean doubling

time of cancers is 74 days for epidermoid tumors and 100 days for adenocarcinomas. Studies of cell kinetics have shown that the doubling time is affected by loss of new tumor cells, which may be as high as 50 to 95%, and by existence of a nonproliferating fraction, which may begin to divide after depletion of actively dividing cells by therapy. Pulmonary cancers are very often accompanied by nonspecific depression of the immunological system; in humans they seem to contain a specific antigen. Nonspecific immunostimulation seems to be a useful adjunct to chemotherapy and specific immunotherapy. In the area of therapeutic strategy, it has been found that nonproliferating cells may be made to proliferate by administration of certain substances, such as nitrogen mustard, endoxan, and mitomycin C. Then there is an optimal interval of 6 to 10 days, depending on the rate of growth, after which drugs which act on proliferating cells should be administered. The author outlines protocol for international cooperation in pulmonary cancer research. (29 references)

- 1818 EXPERIMENTAL RADIATION CARCINOGENESIS. (E.) Walburg, H. E., Jr. (Biol. Div., Oak Ridge Natl. Lab., Tenn.). *Advances in Radiation Biology*, New York, Academic Press, 1974, pp. 210-253.

The present state of knowledge of some of the basic principles of experimental radiation carcinogenesis which could lead to a better predictability of radiation effects in man is reviewed. General considerations regarding the significance of animal data for radiation carcinogenesis include the role of animal experiments in predicting radiation carcinogenesis in man, general theories of radiation carcinogenesis, initiating and promoting mechanisms, the importance of radiation carcinogenesis for the life-shortening effects of radiation, a statistical analysis of specific disease incidences in survival experiments, and special problems of internal emitters. Other topics discussed are tissues at risk from external radiation and internal emitters, dose-effect relationships, relative biological effectiveness, the effect of dose rate, the dependence of sensitivity on age, and differences in sensitivity between strains and species. From the limited human data available, interpretations and qualitative generalizations are offered. (233 references)

- 1819 POSSIBLE VIRAL AETIOLOGY OF HUMAN BREAST CANCER. (E.) Moore, D. H. (Inst. Med. Res., Camden, N.J.). *Br J Cancer* 28(1):88-89, 1973. (11 references)

- 1820 THE POSSIBLE ROLE OF CHEMICAL CARCINOGENS. (E.) Magee, P. N. (Middlesex Hosp. Med. Sch., London, England). *Br J Cancer* 28(1):89-90, 1973. (No references)

- 1821 CANCER: REGRESSIVE EVOLUTION. (E.) Schwind, J. V. (Sansum Res. Fdn., Santa Barbara, Calif.). *Cancer Cytol* 13(1), 1973. (No references)

1822 A SURGEON'S VIEW OF ENVIRONMENTAL FACTORS
IN HUMAN MAMMARY CANCER. (E.) Anderson,
J. M. (Roy. Infirm., Glasgow, Scotland). *Br J Cancer*
28(1):90, 1973. (No references)

1823 SOLAR RADIATION AND SKIN CANCER. (E.)
Johnson, B. E. (Dept. Dermatol., U. Dundee,
Scotland). *Br J Cancer* 28(1):91, 1973. (No references)

1824 CANCER OF THE GASTROINTESTINAL TRACT: EN-
VIRONMENTAL FACTORS IN ALIMENTARY CANCER.
(E.) Gillis, C. R. (Dept. Epidemiol., Preventive
Med., U. Glasgow, Scotland). *Br J Cancer* 28(1):92-
93, 1973. (No references)

1825 BACTERIA AND THE AETIOLOGY OF HUMAN CANCER.
(E.) Hill, M. J. (St. Mary's Hosp. Med.
Sch., London, England) and D. S. Drasar. *Br J Cancer*
28(1):94, 1973. (12 references)

1826 IMMUNOGLOBULINS AND BACTERIA IN THE HUMAN
STOMACH. (E.) Shearman, D. J. C. (Roy.
Infirm., Edinburgh, Scotland). *Br J Cancer* 28(1):
94-95, 1973. (6 references)

- 1827 EFFECTS OF PARTIAL HEPATECTOMY ON CARCINOGENICITY, METABOLISM, AND BINDING TO DNA OF ETHYL CARBAMATE. (E.) Pound, A. W. (Dept. Pathol., U. Queensland, Brisbane, Australia) and T. A. Lawson. *J Natl Cancer Inst* 53(2):423-429, 1974.

Male and female random-bred "Hall" and "Crackenbush" mice were injected with ethyl carbamate (20 or 25 mg s.c.) at various intervals after 1/3 or 2/3 hepatectomy. The incidence of hepatocellular tumors was increased after partial hepatectomy and correlated with the number of cells synthesizing DNA at the time of injection and the number of cells in mitosis. Partial hepatectomy did not affect the numbers of lung tumors or liver hemangiomas, or the number and character of skin tumors if the ethyl carbamate treatment was followed by a promoting treatment with croton oil. Hepatocellular tumors were more common in males, but no sex differences were observed in the number of liver hemangiomas, lung adenomas, or skin tumors. The binding of an ethyl carbamate metabolite to the liver DNA was 14 times greater in the males compared with the females, but the level of binding to lung and epidermal DNA showed no sex differences. Binding was determined by dividing the specific activity of extracted DNA by the specific activity of $2\text{-}^3\text{H}$ ethyl carbamate (50 μC , 20 mg, i.p.). Partial hepatectomy increased the binding to liver DNA in both sexes, but did not alter the amount bound to the lung or epidermal DNA. The rate of metabolism of ^{14}C -ethyl carbamate, determined by rate of $^{14}\text{CO}_2$ elimination was slower after partial hepatectomy, but this did not create a significant increase in the effective dose. The data indicate that the carcinogenic activity of ethyl carbamate is mediated by a metabolic event and that the active metabolite is formed and taken up in the affected cells rather than circulated.

- 1828 INDUCTION OF COLONIC CANCER IN THE RAT BY A SINGLE INJECTION OF 1,2-DIMETHYLHYDRAZINE. (Fr.) Martin, M. S. (Fac. Med., Dijon, France), F. Martin, E. Justrabo, J.-F. Knopf, H. Bastien and S. Knobel. *Biol Gastroenterol (Paris)* 7(1):37-42, 1974.

A single injection of 40 mg/kg s.c. 1,2-dimethylhydrazine (DMH) induced intestinal adenocarcinoma in inbred BD IX rats. Immediately prior to injection, the carcinogen was dissolved in demineralized water at a concentration of 9 mg/ml. Disodium EDTA (2 mg/ml) was added to stabilize the DMH, and the pH was adjusted to 6.6 by addition of sodium bicarbonate. Thirteen male and female rats were treated at the age of 1 day, 9 at 10 days, and 14 at 30 days. Rats were weighed once a week and sacrificed when they showed a significant weight loss, a decline in general condition, or serious intestinal disorders. Animals in each group eventually died of pulmonary infections. Sacrificed animals were carefully autopsied, and a diagnosis of colonic cancer was only made when the lesions invaded the muscular tunic. Localized anomalies of the mucosa were classified as hyperplasia when the normal structure of the glands was preserved and as dysplasias in the case of cellular or glandular atypia. A certain number of these dysplasias could correspond to intramucosal cancers.

The incidence of carcinoma and hyperplasia or dysplasia of the duodenum, jejunum, and colon varied with the time of DMH treatment. A total of 21 carcinomas was observed in 11 rats, 8 dysplasias in 5 rats, and 6 hyperplasias in 6 rats. The mean survival time was 486 days, but significant variation was observed, depending on the age at which the animals were treated. Extraintestinal lesions were observed in several animals. One gastric glandular hyperplasia; one adenoma and one cavernous hemangioma of the liver; one fibrosarcoma and one dysgenetic tumor of the kidney; and one adenoma of the salivary glands were observed. No tumors of the central nervous system or of the external auditory canal were found. However, infectious pulmonary or renal lesions, cystic dilatations of the biliary tract, and degenerative granulomatous lesions of the liver occurred fairly often.

- 1829 CANCER OF THE PANCREAS INDUCED IN THE SYRIAN GOLDEN HAMSTER. (E.) Pour, P. (U. Nebraska Med. Ctr., Omaha), F. W. Druger, J. Althoff, A. Cardesa and U. Mohr. *Am J Pathol* 76(2):349-358, 1974.

Diisopropanolnitrosamine (DIPN 125, 250, or 500 mg/kg) was administered s.c. to 8-wk-old random-bred Syrian golden hamsters once weekly for life. Animals in all dose groups developed pancreatic adenomas within 44 wk. Ductal-type pancreatic adenocarcinomas were found in 90% of the females and 100% of the males in the 500-mg/kg dose group, 94% of the males and females in the 250-mg/kg dose group, and 95% of the females and 80% of the males in the 125-mg/kg dose group. Acinar type pancreatic adenocarcinomas developed in 5% of the females and 6% of the males in the 500-mg/kg dose group, 17% of the females and 6% of the males in the 250-mg/kg dose group, and in none of the 125-mg/kg dose group. The first tumors appeared 15-16 wk from the start of the experiment. The tumors were frequently multiple, with 51% being grossly observable. Invasions of the peritoneum, perineural lymphatics, blood vessels, regional lymph nodes, spleen, and stomach occurred in 18% of the hamsters, while metastases in the liver and lungs were seen in some animals. Fourteen percent of the pancreatic tumor-bearing animals had hemorrhagic ascites, and 72-100% had simultaneous tumors of other sites. Wt loss occurred in all treated hamsters.

- 1830 INDUCTION OF URINARY BLADDER TUMORS BY INTRAVESICULAR INSTILLATION OF BUTYL(4-HYDROXYBUTYL)NITROSAMINE AND ITS PRINCIPAL URINARY METABOLITE, BUTYL(3-CARBOXYPROPYL)NITROSAMINE IN RATS. (E.) Hashimoto, Y. (Tokyo Biochem Res. Inst., Japan), K. Suzuki and M. Okada. *Gann* 65(1):69-73, 1974.

The induction of papillomas and carcinomas of the urinary bladder of female ACI/N rats by the intravesicular instillation of butyl(4-hydroxybutyl)-nitrosamine (BBN) and butyl(3-carboxypropyl)nitrosamine (BCPN) is described. For the experiments, 2% solution of BBN or a 2.5% solution of BCPN, neutralized with NaOH, was used. Each rat received 0.2 ml

of a test solution or distilled water three times/week for 20 weeks; once a week, each rat received an intravesicular injection of 0.2 ml Kanamycin solution to prevent infection. Urinary bladder papillomas were observed in 5 of 7 rats treated with BBN, 6 of 8 treated with BCPN, and in none of 5 injected with distilled water. In many cases transitional cell carcinomas accompanied the papillomas. Besides urinary bladder tumors, 3 rats developed papillomatous hyperplasia of the kidney at the pelvic area, but tumors were not detected in any other organs. The effect of minor metabolites, if any, from BBN or BCPN which are absorbed from the urinary bladder cannot be ruled out.

1831 A NEW METHOD FOR PRODUCING ADENOCARCINOMAS IN THE STOMACH OF DOGS WITH N-ETHYL-N'-NITROSOGUANIDINE. (E.) Kurihara, M. (Dept. Gastroenterol., Juntendo U., Japan), H. Shiradabe, T. Murakami, A. Yasui, T. Izumi, M. Sumida and A. Igarashi. *Gann* 63(2):163-177, 1974.

Well-advanced adenocarcinomas were produced in the stomachs of dogs with a solution of N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) with 2% Tween-60 and a device for bringing the chemical into lasting contact with the stomach mucosa. The ENNG solution was administered twice daily in the diet for 8 months, the total dose being 14.2 g in males and 7.6 g in females. Biopsies confirmed the production of adenocarcinomas within 176-213 days. Within 12 months, radiographic and endoscopic examination revealed tumors in the subcardia and antrum of all dogs still living. The experimental adenocarcinomas metastasized to the pancreatic and thoracic lymph nodes; there were no sarcomatous lesions in the gastrointestinal tract. Although ENNG is probably a less reactive carcinogen than N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), this method of producing stomach tumors in dogs offers several advantages over the earlier method of administering MNNG in the drinking water.

1832 LACK OF TOXICITY AND CARCINOGENICITY OF SOME COMMONLY USED CUTANEOUS AGENTS. (E.) Stenback, F. (U. Nebraska Med. Ctr., Omaha) and P. Shubik. *Toxicol Appl Pharmacol* 30(1):7-13, 1974.

The potential carcinogenicity and toxicity of several commonly used cutaneous agents (benzophenone, propylene glycol, isopropyl myristate, resorcinol, 2-ethyl-1,3-hexanediol, *p*-aminobenzoic acid, and pyrogallol) were studied in female Swiss mice by administering repeated applications of the chemicals on the skin for the life-span of the animals. Tumors seen in both control and treated animals were mainly lymphomas, hemangiomas of the liver, and lung adenomas, as well as tumors of other organs. A statistically significant increase in tumor incidence caused by the chemical treatment was not seen. Skin lesions, slight inflammation, and ulceration were seen, but no persistent cutaneous abnormalities occurred. A few skin tumors were seen in treated areas as well as in untreated areas and in control animals. Thus a carcinogenic or toxic potential which would affect the use of these agents in man was not detected.

1833 AFLATOXIN AND TRICHOHECENE TOXINS: SKIN TUMOR INDUCTION AND SYNERGISTIC ACUTE TOXICITY IN WHITE MICE. (E.) Lindenfelser, L. A. (North. Regional Res. Lab., Agr. Res. Service, Peoria, Ill.), E. B. Lillehoj and H. R. Burmeister. *J Natl Cancer Inst* 52(1):113-116, 1974.

Toxic interactions of three naturally occurring mycotoxins were examined by the mouse skin tumor test and acute toxicity trials. Aflatoxin B₁ (B₁) functioned as a tumor-initiating substance; a single 25-μg dose applied before croton oil as promoter caused papilloma formation on more than half of eight animals. Neither *Fusarium* toxin, trichothecene-2 toxin (T-2) or diacetoxyscirpenol, served as initiating agents. These two mycotoxins acted as weak promoter substances on 7,12-dimethylbenz[*a*]anthracene (DMBA)-initiated mouse skin cells but not on mice treated with B₁ as initiator. Either DMBA or B₁ initiation followed by T-2 promotion (25 μg/dose) caused extensive skin damage and subsequent tolerance of the treated skin to elevated doses of T-2. In acute toxicity trials, combinations of B₁ and T-2 produced a synergistic lethal response.

1834 CATALYSIS OF THE REACTION OF AMINOPYRINE AND NITRITE BY THIOCYANATE. (E.) Boyland, E. (London Sch. Hyg. Tropical Med., England) and S. A. Walker. *Arzneim Forsch* 24(8):1181-1184, 1974.

Aminopyrine reacts quickly with nitrous acid to yield the carcinogen dimethylnitrosamine in a reaction catalyzed by thiocyanate which is present in saliva. Because the concentration of thiocyanate in saliva of smokers is much higher than in nonsmokers, the carcinogenic hazard from aminopyrine would be even greater in smokers than nonsmokers. Aminopyrine must be considered a potential carcinogen because of this reaction and, although it is an effective antipyretic and analgesic drug, this is a cogent reason for its prohibition in medical use.

1835 FREE RADICAL INDUCED IN RAT LIVER BY A CHEMICAL CARCINOGEN, N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Nagata, C. (Biophysics Div., Natl. Cancer Ctr. Res. Inst., Tokyo, Japan), Y. Ioki, M. Kodama and Y. Tagashira. *Ann NY Acad Sci* 222:1031-1047, 1973.

A nonenzymatic free-radical having a characteristic electron spin resonance (esr) signal ($g = 2.039$ and 2.015) was obtained after mixing the potent carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 5 mg) with rat liver supernatant. NADH or NADPH was necessary for formation of the free radical, but EDTA and citric acid inhibited it. The esr signal of the free radical was similar to that previously obtained from the livers of rats fed such hepatic carcinogens as 2-acetylaminofluorene (AAF) and *p*-dimethylaminoazobenzene (DAB); in the latter case, the origin of the signal was identified a paramagnetic complex (NO-Fe-thiol). Thus, in the present case, the NO-group released from the MNNG combined with some components in the liver supernatant. Par-

icipation of an SH-group in the free-radical formation was demonstrated: the same esr signals were obtained by mixing sulfhydryl compounds with MNNG in aqueous FeCl_2 solution. Free-radical formation was greatly reduced after Sephadex G-50 column chromatography, but the fast-eluted fraction regained this activity after the addition of FeCl_2 . Of 11 enzymes tested, xanthine oxidase and diaphorase produced the free radical. No signal was observed when AH-130 hepatoma supernatant was mixed with MNNG, while signals from regenerating livers were nearly the same as that of normal liver and the signal from the livers of tumor-bearing rats was diminished. A similar free radical was produced by mixing MNNG with stomach mucosa supernatant; it was also formed after mixing N-methyl-N-nitrosourea and N-methyl-N-nitrosourea with liver supernatant. After, but not before, photoirradiation, N-nitrosodimethylamine, N-nitrosodiethylamine, N-nitrosopiperidine, and N-nitrosomorpholine also produced free radical with the characteristic esr signal.

- 1836 CARCINOGENICITY OF PROCARBAZINE. (E.) Deckers, C. (Cancer Inst., Catholic U., Louvain, Belgium), L. Deckers-Passau, J. Maisin, J. M. Gauthier and F. Mace. *Z Krebsforsch* 81(2):79-84, 1974.

Procarbazine (15 mg/wk) was administered i.p. to 6-wk-old female R strain rats of Wistar origin; the animals received a total dose of 225 mg over a period of 7.5 months. A total of 13 malignant tumors and one benign tumor were observed in the 10 treated animals, each animal developing at least one tumor with a mean latency of 301 days. The most commonly observed tumors were mammary tumors, which developed after a median latent period of 270 days. They did not metastasize or deeply invade the surrounding tissues. Uterine tumors developed with a median latency of 377 days; no distant metastases were observed, but local intraperitoneal dissemination was seen. Two rats developed ear duct tumors after a latent period of 244 days. One malignant squamous cell carcinoma rapidly invaded the skin; the second tumor was a benign hyperplastic nodule. Results show that procarbazine is a potent carcinogen for R-strain female rats.

- 1837 ARSENIC: POISON TURNED CARCINOGEN. (E.) Anonymous. *Science News* 106(10):149, 1974.

A Dow chemical company study showed that about 1/3 of 178 former workers in a Midland, Michigan arsenic plant had died of cancer. An Allied chemical company study showed that of 27 workers who died during the last 13 yr after exposure to arsenic in a plant in Baltimore, 19 died from cancer. Lung and lymphatic cancer rates were six and seven times higher than expected for male workers. Only long-term fairly high-level exposures to inorganic arsenic, a widely used industrial chemical, are implicated in the increased death rates from cancer. The Occupational Safety and Health Administration will conduct hearings on tightening arsenic exposure standard from the present level of 0.5 mg/m^3 to a proposed 0.05 mg/m^3 . Although it is believed that the proposed standard

would definitely reduce the incidence of disease, not all chemical companies support the change. There is some worry about consumer exposure to arsenic in pesticides and in commercial poultry and swine; however, the growth-promoting drugs fed to feedstock are organic arsenicals which have not proven carcinogenic in animals.

- 1838 FINE STRUCTURE OF BOWEN'S DISEASE IN CHRONIC ARSENICALISM. (E.) Yeh, S. (Dept. Path., Natl. Taiwan U., Taipei), H. C. Chen, S. W. How and C. S. Deng. *J Natl Cancer Inst* 53(1):31-44, 1974.

Thirty-five skin biopsy specimens were taken for ultrastructural studies from 30 patients with Bowen's disease due to chronic arsenicalism. The most characteristic changes of the Bowen's lesion, though also occurring in epidermoid carcinoma or basal cell carcinoma, included intact basement membrane; widened intercellular spaces with microvillus-like cytoplasmic projection; a decrease in intercellular desmosomes; many dyskeratotic epithelial cells; many normal and abnormal mitotic figures; the presence of giant cells; numerous intracytoplasmic desmosomes; and vacuolar degeneration of keratinocytes. Three basic types of tumor cells are described and the process of dyskeratosis detailed and illustrated. The mechanisms of developing intracytoplasmic desmosomes and vacuoles are postulated. Melanocytes including mitotic figures, Langerhans' cells, and Merkel cells are also described.

- 1839 GENETIC EXPRESSION OF ARYL HYDROCARBON HYDROXYLASE ACTIVITY. INDUCTION OF MONOOXYGENASE ACTIVITIES AND CYTOCHROME P_1 -450 FORMATION BY 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN IN MICE GENETICALLY "NONRESPONSIVE" TO OTHER AROMATIC HYDROCARBONS. (E.) Poland, A. P. (U. Rochester Sch. Med. Dent., N.Y.), E. Glover, J. R. Robinson and D. W. Nebert. *J Biol Chem* 249(17):5599-5606, 1974.

The i.p. administration of aromatic hydrocarbons such as 3-methylcholanthrene, β -naphthoflavone, or naphthacene induces several monooxygenase activities and the new formation of a spectrally distinct CO-binding cytochrome in genetically "responsive" inbred mouse strains, but fails to induce these changes in genetically "nonresponsive" inbred strains even at chronically high doses. Administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, 40 $\mu\text{g}/\text{kg}$), however, causes induction of a similar magnitude in either "responsive" or "nonresponsive" mice of several monooxygenase activities and the new formation of cytochrome P_1 -450 in liver, bowel, lung, kidney, and skin. Application of TCDD (4 μg) to the skin of either "responsive" or "nonresponsive" mice induces aryl hydrocarbon hydroxylase activity more than six-fold in the skin and in the liver. These data demonstrate that genetically "nonresponsive" mice have the structural and regulatory genes necessary for expression of the inducible microsomal monooxygenase activities and associated new formation of

cytochrome P₁-450 and that the defect in these mice is a failure to recognize aromatic hydrocarbons which are less potent inducers.

1840 CHRONIC MYELOID LEUKEMIA OF TOXIC ORIGIN. (Fr.) Curtes, J. P. (Anti Poisons Ctr., C.H.R., Rennes, France), M. Le Marec, D. Guerin and P. Michaux. *J Eur Toxicol* 6(6):306-308, 1973.

A 47-yr-old worker was diagnosed as having chronic myeloid leukemia after four yr of occupational exposure to solvent vapors containing 55 ppm of toluene. The patient spent only 10% of his total working hours in this shop and had been transferred to another job two yr prior to development of leukemia. He was hospitalized in 1970 with hepatosplenomegaly; an increased WBC (300,000); 37% polynuclear neutrophils; 63% myeloblasts, myelocytes, and metamyelocytes; an erythrocyte sedimentation rate of 60 mm during the first hour; elevated gamma-globulins; and other signs confirming the diagnosis. The Philadelphia chromosome was not found, but alkaline phosphatase activity was significantly decreased. Antimitotic therapy gave a remission which lasted for two months. Drugs were used to treat a series of exacerbations and, after two and a half yr, splenic cobalt therapy was administered. After a very brief improvement, the patient's condition became terminal in October, 1972 with thrombocytopenia and a cerebromeningeal hemorrhage which caused death. Chronic myeloid leukemia of the same type was diagnosed in the patient's wife in November, 1971, with Philadelphia chromosome present in every cell analyzed. After treatment, remission was apparently complete. This casts some doubt about whether toluene actually caused leukemia in her husband. Although there are eight reports in the literature on blood diseases in married couples, this is the first report of chronic myeloid leukemia which is probably toxic in origin developing in a married couple.

1841 GASTRIC CARCINOGENESIS IN RAT INDUCED BY METHYLNITROSOUREA (MNU): MORPHOLOGY, AND HISTOCHEMISTRY OF NUCLEASES. (E.) Fort, L. (Dept. Gen. Pathol. Neuropathol., U. Louvain, Belgium), H. S. Taper and J. M. Brucher. *Z Krebsforsch* 81(1):51-62, 1974.

Random-bred male Wistar R strain rats were given 5/mg/kg/day of methylnitrosourea (MNU) by gastric intubation 4-5 times weekly for 134 days or 2-3 times weekly for 180 days; the total doses of MNU were 435 mg/kg in the first group and 350 mg/kg in the second group. MNU was also administered p.o. (5 mg/kg) or i.p. (10, 20, 30, or 40 mg/kg) in a single dose to pregnant Wistar R rats. Twenty-seven squamous cell carcinomas of the forestomach, two adenocarcinomas of the glandular stomach, and numerous preneoplastic lesions of the mucosa in both parts of the stomach were observed in the 190 chronically treated animals. Single transplacental administration did not produce any gastric tumors. However, preneoplastic alterations were detected in the forestomachs of 42 and in

the glandular stomachs of 25 of the 51 animals examined; the histologic patterns were similar to those observed in the chronically treated rats. The preneoplastic and neoplastic changes in the forestomach showed distinct decreases in the levels of acid and alkaline DNase and RNase activities compared with normal nontreated forestomachs. The results support the hypothesis that nuclease deficiency precedes or facilitates carcinogenesis.

1842 LIVER TUMOURS IN CF-1 MICE EXPOSED FOR LIMITED PERIODS TO TECHNICAL DDT. (E.)

Tomatis, L. (Int. Agency Res. Cancer, Lyon, France), V. Turusov, R. T. Charles, M. Boiocchi and E. Gati. *Z Krebsforsch* 82(1):25-35, 1974.

CF-1 mice were given 250 ppm of DDT mixed into the diet for 15 or 30 weeks and killed at different time intervals. Following 30 weeks of treatment a similar proportion of male mice bearing hepatomas was observed at 65, 95, and 120 weeks from the beginning of the experiment. In females the incidence of hepatomas increased from the 65th to the 95th week. A similar pattern was observed in mice exposed for 15 weeks, but the incidence of hepatomas was much lower than after 30 wk exposure. The storage levels of DDT and metabolites were measured in the liver and interscapular fat. Similar storage levels were found after 15 or 30 weeks of treatment. The levels decreased markedly after the cessation of the treatment, but even after 90 weeks they were higher than in untreated controls. These findings show that the hepatocarcinogenicity of DDT is dose-related, and indicate that DDT-induced hepatomas do not regress but continue to grow after cessation of the treatment.

1843 THE *IN VITRO* FORMATION OF N-NITROSAMINES IN THE RAT BLADDER AND THEIR SUBSEQUENT ABSORPTION. (E.) Hawksworth, G. (St. Mary's Hosp. Med. Sch., London, England) and M. J. Hill. *Br J Cancer* 29(5):353-358, 1974.

Normal hamsters and Sprague-Dawley rats and Sprague-Dawley rats with *Escherichia coli*-induced bladder infections were treated with various amines and nitrosamines introduced by gastric intubation or into the bladder via catheters. The rats were given water containing 5 mg/ml sodium nitrate, of which 90% was excreted in the urine. After 4 days on this schedule, piperidine hydrochloride or pyrrolidine (500 µg) was administered by gastric intubation. The urine of 50% of the animals with bladder infections contained nitrosamine, while none of the control samples did. Similar results were obtained *in vitro* with the same dose of amine in a broth culture. When ¹⁴C-dimethylamine hydrochloride (DMN) was introduced into the bladder, the radioactivity was rapidly absorbed into the circulating blood. After 4 hr, 8% of the total dose was in the blood, 33% was in the urine, and 8% was found in the major organs, especially the liver, stomach and kidney; there was no difference between control and infected animals. Four hr after the administration of ³H-N-nitrosopiperidine (NNP), 1% of the administered

dose was found in the blood, and 4% was found in the major organs, particularly the liver and kidney. The distribution of radioactivity in the hamster after ^3H -NNP administration was different; the amount of radioactivity in the liver and kidney being equal, with substantial amounts being found in the stomach, small intestine, and lungs. The amount of nitrosamine introduced into the bladder ranged from 2.5-5 μg , which is approximately the amount which would be expected to be formed in human urine. Thus, the degree of absorption may indicate the extent to which the absorption of nitrosamines from the human bladder would occur.

- 1844 THE LONG-RANGE IMPACT OF ASBESTOS EXPOSURE.
(E.) Golden, R. L. (East Northport, N.Y.).
Int J Occup Hlth Safety 43(1):18-19, 1974.

A case history of a 48-yr-old man with a history of five episodes of recurrent right pleural effusion is presented. Past history was significant for diabetes mellitus and hypertension. In addition, he gave a history of working for 7 months from 1941 to 1942 as a welder and driller in a shipyard with exposure to asbestos. Thoracentesis in 1967 showed negative cytology. Tuberculin test at this time was positive; however, repeated cultures and smears were unrewarding. Cell block of pleural fluid obtained in 1969 showed "slightly atypical" mesothelial cells. Right pleural needle biopsy was unrewarding. Exploratory laparotomy in 1972 revealed multiple small implants over the right pleura and diaphragm. Histologic examination showed infiltrating tumor consistent with malignant mesothelioma. The patient exhibited the "crooked-posture sign" in that he leaned toward the affected side and had an associated dorsal scoliosis. Thus, malignant mesothelioma must be suspect in patients with recurrent pleural effusions of unknown etiology.

- 1845 EFFECT OF NITROFURANS ANTAGONISTIC TO 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE IN HEPATOCARCINOGENESIS AND RNA POLYMERASE ACTIVITY OF LIVER CELL NUCLEI IN RATS. (E.) Akao, M. (Inst. Chemobidynamics, Chiba U., Japan), K. Kuroda, Y. Tsutsui, M. Kanisawa and K. Mivaki. *Cancer Res* 34(8):1843-1850, 1974.

Two nitrofurans, 2-(2-furyl)-3-(5-nitro-2-furyl)-acrylamide (N1) and 2-amino-5-[2-(5-nitro-2-furyl)-1-(2-furyl)vinyl-1]-1,3,4-oxadiazole (N2), were studied for their effect on 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB)-induced hepatocarcinogenesis and on liver nuclear RNA polymerase activity changes in male and female Donryu rats. Studies were conducted on rats fed 3'-Me-DAB (0.06%; total dose 0.5 or 1.0 g) and N1 or N2 (0.2%; total dose 3.34 g) simultaneously and on rats fed 3'-Me-DAB followed by feeding with N1 or N2 (total dose 1.67 g). Simultaneous N1 or N2 feeding reduced the incidence of hepatoma development by 80% compared with controls fed only 3'-Me-DAB. A similar reduction was observed in rats fed 3'-Me-DAB followed by N1 or N2. Simultaneous or followed feeding of N1 or N2

was able to delay or prevent 3'-Me-DAB induced reduction of liver nucleus Mn^{++} -(NH_4) $_2\text{SO}_4$ - and Mg^{++} -activated RNA polymerase. Followed feeding of N1 or N2 promoted recovery of 3'-Me-DAB-induced changes in RNA polymerase activity and liver nucleic acid content. These findings indicate that nitrofurans could retard 3'-Me-DAB carcinogenesis by exhibiting an effect antagonistic to that of 3'-Me-DAB on rat liver.

- 1846 BIOLOGICAL EFFECTS OF ASBESTOS. (E.)
Anonymous. *Lancet* (7882):706, 1974.

At a time of increased demand for asbestos products, the hazards of industrial asbestos exposure with respect to lung and pleural cancers is being recognized. Asbestosis and bronchial carcinoma appear to be produced by all types of asbestos fibers, with a definite dose-response relationship. However, production of human mesotheliomas is closely related to exposure to crocidolite fibers. Injection of all types of fibers into the pleural cavity of laboratory animals induces mesotheliomas, while in man only the crocidolite fibers penetrate effectively on inspiration. Glass or aluminum oxide fibers having dimensions similar to those of asbestos fibers are also capable of experimentally inducing mesotheliomas. This suggests that the physical properties rather than chemical composition may be the important factor. Chemical carcinogens have been shown to act synergistically with asbestos fibers in inducing bronchial carcinomas in animals.

- 1847 ASBESTOS INDUCED SELECTIVE RELEASE OF LY-SOSOMAL ENZYMES FROM MONONUCLEAR PHAGOCYTES. (E.) Daview, P. (MRC Clin. Res. Ctr., Harrow, Middlesex, England), A. C. Allison, J. Ackerman, A. Butterfield and S. Williams. *Nature* 251(5474):423-424, 1974.

The total amount of lysosomal enzymes was measured in mouse peritoneal mononuclear phagocyte (MP) cultures after 24 hr of exposure to asbestos (chrysotile A, 1-50 $\mu\text{g}/\text{ml}$). While there were no significant changes in the total concentration of lysosomal enzymes in the MP cultures, there was a significant increase in the proportion of enzymes in the culture medium compared with the cells. This increase was directly proportional to the asbestos concentration, as was the absolute amount of enzyme activity in the culture medium. Asbestos exposure significantly elevated the concentrations of the two nonlysosomal enzymes, lactate dehydrogenase and leucine-2-naphthylamidase, in the cells. The selective release of lysosomal enzymes caused by asbestos was time dependent, being nonsignificant after 3 hr of exposure and rising rapidly and progressively after 4.5 hr of exposure. The delay in release is probably due to the coating of ingested asbestos fibers with plasma proteins. Asbestos also produces an intense granulomatous reaction after i.m. injection in mice. The data support the possibility that the selective release of lysosomal enzymes from MP by asbestos may be responsible for certain aspects of the tissue damage seen in chronic inflammation.

Persons occupationally exposed to asbestos might be injected with a granuloma-inducing material other than asbestos to maintain a local granulomatous reaction which might prevent the appearance of mesotheliomas and bronchogenic cancer.

1848 EFFECT OF PROTEIN DEFICIENCY ON THE INDUCIBILITY OF THE HEPATIC MICROSOMAL DRUG-METABOLIZING ENZYME SYSTEM--III. EFFECT OF 3-METHYLCHOLANTHRENE INDUCTION ON ACTIVITY AND BINDING KINETICS. (E.) Hayes, J. R. (Dept. Biochem. Nutr., Virginia Polytech. Inst. St. U., Blacksburg) and T. C. Campbell. *Biochem Pharmacol* 23(12):1721-1731, 1974.

Male, weanling Sprague-Dawley rats divided into three groups were maintained for 15 days on a semipurified diet containing either 5% casein fed *ad lib.* (group 1), 20% casein pair-fed to group 1 (group 2), or 20% casein fed *ad lib.* (group 3). The animals were injected i.p. days 13 and 14 with either corn oil or 3-methylcholanthrene (3-MC) (20 mg/kg) in corn oil. Twenty-four hr after the last injection, the animals were decapitated and liver microsomes were prepared. Ethylmorphine (EM) metabolism was decreased by both protein deficiency and 3-MC induction, whereas aniline (AN) metabolism was decreased by protein deficiency but increased by 3-MC treatment. Protein deficiency reduced both cytochrome *c* and P-450 reductase activities, whereas 3-MC treatment did not alter these parameters. The most significant aspect of these studies was that even though the microsomal enzyme system of protein-deprived animals could be induced, the induced activity never reached that of the protein-sufficient controls.

1849 ABERRANT REGENERATION IN CARCINOGEN-TREATED EARTHWORMS (*EISENIA FOETIDA*). (E.) Andrews, E. J. (Milton S. Hershey Med. Ctr., Pa.). *J Exp Zool* 189(3):333-338, 1974.

Groups of earthworms (*Eisenia foetida*) were injected with 1% methylcholanthrene (MCA), 0.5% 7,12-dimethylbenz(a)anthracene (DMBA), or 3×10^{-4} mg of N-methyl-N-nitrosoguanidine (MNNG). After one wk, the posterior ten segments were removed from all worms. Twenty-five days after amputation the number of regenerated segments were counted. A statistically significant overgrowth of segments occurred in MCA-treated worms as compared with controls. DMBA treatment failed to alter the number of regenerating segments and worms treated with MNNG had statistically fewer regenerating segments than controls. An overgrowth of segments also occurred in certain groups of vehicle-injected control worms. The groups receiving oil-based vehicles had significantly greater growth than Hank's Balanced Salt Solution injected controls. A new theory of the mechanism of regeneration is offered to explain the seemingly paradoxical results. It is hypothesized that the immune response in invertebrates is the stimulating factor for regeneration and that this characteristic has survived through evolution in the form of immunostimulation of the vertebrate vestige of the blastema: the neoplasm.

1850 A NEW HYPOTHESIS CONCERNING THE REACTIVE SPECIES IN CARCINOGENESIS BY 7,12-DIMETHYLBENZ(a)ANTHRACENE. THE 5-HYDROXY-7,12-DIMETHYLBENZ(a)ANTHRACENE-7,12-DIMETHYLBENZ(a)ANTHRACENE-5(6H)ONE EQUILIBRIUM (E.) Newman, M. S. (Dept. Chem., Ohio State U., Columbus) and D. R. Olson. *J Am Chem Soc* 96(19):6207-6208, 1974.

Attempts to prepare 5-hydroxy-7,12-dimethylbenz(a)-anthracene (5-HO-7,12-DMBA) from 7,12-dimethylbenz(a)anthracene (DMBA) showed that it exists as a mixture of DMBA-5(6H)one and 5-HO-7,12-DMBA. Further studies on the conversion of hydroxy to methoxy compounds suggested that the benzanthracene phenols rapidly tautomerized to the ketonic tautomers which added methanol to form hemiketals which then lost water to yield the methyl ethers. The tendency for the hydroxy isomers to exist in the keto form was explained by steric strain due mainly to the 12-methyl group. The fact that DMBA-5(6H)one, the keto form, was very reactive may be of significance in carcinogenesis by DMBA with carcinogenic metabolism probably involving the 5-position in 7-methylbenz(a)anthracene and DMBA. It is suggested that the reactive intermediate in the case of DMBA may be the ketonic substrate DMBA-5(6H)one, which in principle could readily be formed from an epoxide precursor or some alternate intermediate.

1851 INDUCTION OF TUMORS IN THE STOMACH AND DUODENUM OF HAMSTERS BY N-ETHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Kawachi, T. (Nat'l. Cancer Ctr. Res. Inst., Tokyo, Japan), K. Kogure, N. Tanaka, A. Tokunaga, S. Fujimura, T. Sugimura, N. Kuwabara and S. Takayama. *Z Krebsforsch* 81(1):29-36, 1974.

N-Ethyl-N'-nitro-N-nitrosoguanidine (ENNG) (91 µg/ml) was administered in the drinking water of 6-wk-old male golden hamsters continuously for 12 months. The ENNG-treated animals grew at almost the same rate as the nontreated controls until day 108, after which they continued to grow at a slower rate. Seven of 20 treated animals died of pneumonia within 7 months; they had no tumors. The first tumor was observed on day 253. Six adenocarcinomas of the glandular stomach, six adenocarcinomas of the duodenum, three squamous cell carcinomas (forestomach and epipharynx), one fibrosarcoma of the peritoneal cavity, and two multiple papillomas of the forestomach developed in the 13 hamsters surviving more than 36 weeks. ENNG is more suitable than N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) for use in the induction of epithelial tumors in the alimentary tract of hamsters and dogs.

1852 STRAIN- AND AGE-DEPENDENT TRANSPLACENTAL CARCINOGENESIS BY 1-ETHYL-1-NITROSOUREA IN INBRED STRAINS OF MICE. (E.) Diwan, B. A. (Jackson Lab., Bar Harbor, Maine) and H. Meier. *Cancer Res* 34(4):764-770, 1974.

Pregnant AKR/J, SWR/J, DBA/2J, C57BL/6J, and C57L/J mice were given a single i.p. injection of 1-ethyl-

1-nitrosoarene (ENU), 0.5 mmole/kg, in trioctanoin on either day 12, 14, 16, or 18 of gestation. Tumors developed in offspring of all strains, but the incidence, type, and latency period depended on both the inbred strain and the specific day of gestation. The most common tumors were single or multiple pulmonary adenomas and leukemias after exposure to ENU on days 16 and 18, resp. These two types of tumor were frequently concurrent, but each was found simultaneously with other tumor types as well. SWR/J mice were most susceptible to pulmonary adenomas; leukemia incidence was significantly high in SWR/J and DBA/2J mice as well as in the leukemia-prone AKR/J strain. Aside from thymic or splenic leukemias and pulmonary adenomas, other tumor types were hepatomas, Harderian gland adenomas, tumors of endocrine glands, particularly the ovary, and even neurogenic tumors. Hepatomas occurred preferentially in males, especially DBA/2J males.

1853 TUMOR INDUCTION WITH A SINGLE ADMINISTRATION OF N-2-FLUORENYLACETAMIDE OR N-HYDROXY-2-FLUORENYLACETAMIDE TO NEWBORN MICE: EFFECT OF AGE AFTER BIRTH. (E.) Fujii, K. (Inst. Hygiene Sci., Tokyo, Japan) and H. Takahashi. *Gann* 65(4):345-349, 1974.

ICR/JCL mice were treated with a single s.c. dose of N-3-fluorenylacetamide (FAA, 50 µg) or N-hydroxy-2-fluorenylacetamide (N-OH-FAA, 25 µg) 12 to 72 hrs after birth. The incidence of liver tumors was 41% in FAA-treated males, 3% in FAA-treated females, 30% in N-OH-FAA-treated males, and 0% in N-OH-FAA-treated females, 6% in control males, and 0% in control females. The liver tumor incidence in the FAA-treated mice did not correspond to the average body wt at the time of injection, whereas the liver tumor incidence in the N-OH-FAA-treated mice did. Most of the tumors were hepatic cell adenomas, with one hepatic cell carcinoma; no metastases were observed. Among the FAA-treated mice, the liver tumor incidence was significantly lower among those injected 12 hrs after birth than among those injected 24-78 hrs after birth. The incidence of pulmonary tumors was the same in the treated and control groups and did not differ according to sex. Six drug-treated mice developed leukemia and one mouse developed a uterine leiomyoma.

1854 OXIDATION OF 7,8,12-TRIMETHYLBENZ(a)ANTHRA-CENE WITH LEAD TETRAACETATE. (E.) Pataki, J. (Ben May Lab. Cancer Res., U. Chicago, Ill.) and R. Balick. *Tetrahedron Lett* (38):3447-3449, 1974.

Attempts were made to prepare 7-hydroxymethyl-8,12-dimethylbenz(a)anthracene (7,12-DMBA) by oxidation of 7,8,12-trimethylbenz(a)anthracene (7,8,12-TMBA) with lead tetraacetate to determine whether the adrenocorticolytic activity of the latter might be explained by steric hindrance of the methyl group at C-7 opposing the enzymatic hydroxylation in the organism. In the reaction of 7,8,12-TMBA with one molecular equivalent of lead tetraacetate in glacial acetic acid, a product was formed which contained

no oxygen but was rather heat sensitive. Purification was effected by repeated filtration of a methylene chloride solution through silica gel. The new hydrocarbon was assigned the structure of 7,12-dimethylene-8-methyl-7,12-dihydrobenz(a)anthracene. When the oxidation was performed with two equivalents of Pb(OAc)₄, the new hydrocarbon was not formed; the normal oxidation product, 7,12-di(acetoxymethyl)-8-methylbenz(a)anthracene was obtained.

1855 CARCINOGENIC EFFECTS OF N-NITROSOMORPHOLINE AND N-NITROPIPERIDINE ON EUROPEAN HAMSTER (*CRICETUS CRICETUS*). (E.) Mohr, U. (Med. Coll., Hannover, West Germany), G. Reznik and H. Reznik-Schuller. *J Natl Cancer Inst* 53(1):231-237, 1974.

Nitrosomorpholine (NM) and nitrosopiperidine (NP) were administered s.c. once weekly at 0.05, 0.1, or 0.2 of the LD₅₀ to captured male and female European hamsters; the treatments were continued throughout the animals' lives. The LD₅₀ of NM was 493 mg/kg for females and 429 mg/kg for males, while that of NP was 226 mg/kg for both sexes. Most of the animals treated with either compound developed multiple primary tumors in more than one organ. These neoplasms were most frequently found in the nasal cavities, the trachea, the lungs, and the upper digestive tract (oral cavity, cheek pouches, and forestomach), in that order. As compared with NP, NM induced tumors of the upper respiratory system in all dosage groups in shorter amounts of time. NM also induced significantly more malignant neoplasms in the nasal cavities and larynx. NP induced more neoplasms of the nasopharyngeal duct (30%) than NM (20%), although NM induced up to 40% more tumors of the trachea. The survival time, degree of malignancy, and number of tumors were dose related.

1856 LIVER-CELL ADENOMAS AND PELIOSIS HEPATIS IN MICE ASSOCIATED WITH OXAZEPAM. (E.) Fox, K. A. (Dept. Biol., State U. New York, Fredonia) and R. B. Lachen. *Res Commun Chem Pathol Pharmacol* 8(3):481-488, 1974.

Oxazepam (0.05% and 0.15%), a benzodiazepine tranquilizer, was administered in the food of male and female Swiss Webster mice; the treatment lasted for nine months, beginning at age three months. The mice then received normal diets for two months prior to being killed. The survival rates of the treated mice did not differ significantly from those of the nontreated controls. At the time of sacrifice, five of eight oxazepam (0.15%)-treated males and eight of 13 oxazepam (0.15%)-treated females had liver tumors. These tumors were generally multiple and the livers were often twice the normal size. Three of the males given the lower dose of oxazepam had small, solitary, pedunculate liver tumors. No metastases were seen in any of the animals. Histologically, all of the tumors were liver-cell adenomas which showed peliosis and extramedullary hematopoiesis. Most of the tumor cells produced small amounts of bile. These lesions resembled those associated with certain forms of steroid therapy in humans.

- 1857 THE CARCINOGENIC EFFECTS OF DIMETHYLNITRO-SOMETHYLUREA IN EUROPEAN HAMSTERS (*CRICETUS CRICETUS* L.) (E.) Mohr, U. (Med. Coll., Hannover, W. Germany), H. Haas and J. Hilfrich. *Br J Cancer* 29(5):359-364, 1974.

Dimethylnitrosamine (DMN) and nitrosomethylurea (NMU) were injected s.c. once weekly for life into male and female wild European hamsters. The dose levels were 0.1, 0.2, or 0.05 of the LD₅₀ for each compound (43 mg/kg for females and 28 mg/kg for males for DMN, and 113 mg/kg for both sexes for NMU). DMN induced malignant hemangioendotheliomas of the liver and kidney, hepatocellular carcinomas of the liver, one squamous cell carcinoma of the nasal cavity, two malignant lymphomas, one rhabdomyosarcoma of the diaphragm, one leiomyosarcoma of the small intestine, one malignant schwannoma, one lung adenoma, and three papillomas of the forestomach. All neoplasms were malignant. The effect of NMU was localized at the site of administration and resulted in s.c. fibrosarcomas, carcinosarcomas, and epidermal carcinomas. With both drugs, survival increased with decreasing dosage.

- 1858 HYDROXAMIC ACIDS FROM THE REACTION OF ACTIVE ACETALDEHYDE WITH AROMATIC NITROSO COMPOUNDS. (E.) Corbett, M. D. (Sch. Pharm., U. Mississippi, University). *Bioorganic Chem* 3(3):361-365, 1974.

A previously unknown organic reaction is reported in which α -hydroxyethylthiamine reacts with nitrosobenzene to produce *N*-phenylacetohydroxamic acid. The product is not a known carcinogen but the possibility exists that such reactions may be operative *in vivo* to form known carcinogens from appropriate nitroso compounds. It is thus possible that carcinogenic hydroxamic acids can be formed from aromatic nitroso compounds via reactions not requiring the intervention of microsomal oxidases.

- 1859 CHANGES IN THE COMPOSITION OF RAT LIVER CHROMATIN FRACTIONS DURING NITROSAMINE CARCINOGENESIS. (E.) Gronow, M. (Dept. Exp. Pathol. Cancer Res., U. Leeds, England) and T. Thackrah. *Eur J Cancer* 10(1):21-25, 1974.

Chromatin fractions were prepared from the nuclei isolated from the livers of control and diethylnitrosamine (DEN)-treated Tuck Wistar SPF rats 70 days after the administration of 3 mg/kg/day. Three fractions containing DNA were obtained after treatment of the nuclei with high pressure followed by ultrasonics. The fractions were labeled by injecting the animals with radioactive RNA and DNA precursors. In the carcinogen-treated animals given tritiated thymidine a three-fold increase in specific activity of the DNA was observed in all fractions. The nonhistone proteins were examined by SDS polyacrylamide gel electrophoresis. A polypeptide with a molecular weight of 17,500 was found to be missing in the euchromatin of DEN-treated liver. The significance of these findings in relation to carcinogenic change remains to be

elucidated but the concomitant loss or large decrease in a nonhistone protein with a molecular weight of 17,500 from one of the fractions could be an important factor in the increased DNA synthesis.

- 1860 RETROSPECTIVE STUDY OF THE ASSOCIATION BETWEEN USE OF RAUWOLFIA DERIVATIVES AND BREAST CANCER IN ENGLISH WOMEN. (E.) Armstrong, B. (Dept. Regius Professor Med., Oxford U., England), N. Stevens and R. Doll. *Lancet* (7882):672-675, 1974.

A retrospective study of 708 breast cancer patients and 1430 control patients with other neoplasms showed an association between breast cancer and the use of rauwolfia derivatives (relative risk 2.0). This association became statistically significant at the 5% level (relative risk 3.9) when other neoplasms previously suggested to be associated with reserpine use were removed from the control group. No association was found between breast cancer and the use of other drugs known to enhance pituitary prolactin release.

- 1861 INDUCTION OF PANCREAS TUMOURS BY DI-ISOPROPANOLNITROSAMINE. (E.) Krüger, F. W. (German Cancer Res. Ctr., Heidelberg, W. Germany), P. Pour and J. Althoff. *Naturwissenschaften* 61(7):328, 1974.

Di-*n*-propylnitrosamine (DPN) is metabolized *in vivo* to a methylating agent (methylpropylnitrosamine) and acetic acid by β -oxidation in analogy to the metabolism of fatty acids. The carcinogenic activity of the postulated intermediates is qualitatively comparable to that of the parent compounds. When both aliphatic chains of DPM are degraded in the same manner, dimethylnitrosamine results with diisopropanolnitrosamine (DIPN) as an intermediate. DIPN was purified from di-isopropanolamine by molecular distillation; no contamination with the corresponding nitrite ester(s) was observed. In less than a year, a high percentage of Syrian golden hamsters treated with DIPN developed benign and malignant neoplasms of the exocrine pancreas; most of these tumors originated in the duct epithelium. Neoplasms were also found in the respiratory system, liver, and kidneys.

- 1862 RESERPINE AND BREAST CANCER. (E.) Jick, H. (Boston U. Med. Ctr., Mass.), D. Slone, S. Shapiro, O. P. Heinonen, S. C. Hartz, O. S. Miettinen, M. P. Vessey, D. H. Lawson and R. R. Miller. *Lancet* (7882):669-671, 1974.

Examination of data from a multipurpose survey carried out in 24 Boston area hospitals during 1972, revealed an association between a positive history of reserpine use and a discharge diagnosis of breast cancer. A more detailed analysis was conducted on 150 newly diagnosed breast cancer patients from this group in whom full information on antihypertensive drug therapy was available. Among the 150

patients, 11 (7.3%) had taken a reserpine-containing drug prior to admission as opposed to only 2.2% of 600 age-matched surgical and 2.2% of 600 age-matched medical patient controls. The rate of exposure to other antihypertensive agents was similar in all three groups. The relative risk for breast cancer in patients who had taken reserpine was 3.5 times that of controls. The results indicated that breast cancer patients had used reserpine for longer periods than controls. No one particular reserpine preparation was implicated.

1863 MUTAGENICITY STUDIES OF SACCHARIN IN MICE. (E.) Sram, R. J. (Inst. Hyg. Epidemiol., Prague, Czechoslovakia) and Z. Zudova. *Bull Environ Contam Toxicol* 12(2):186-192, 1974.

Studies were conducted on ICR male mice treated with single or repeated i.p. injections of saccharin to determine the mutagenicity and, hence, genetic risk of saccharin use. Following treatment, male mice were mated with female mice. The latter were autopsied between day 13-19 of pregnancy and scored for corpora lutea, total number of implants, early and late fetal deaths, and live embryos. Total dominant lethality was calculated from these data. None of the treatment regimens affected male fertility. Treatment with a single dose of 1000 mg/kg or with 5 divided doses of 200 mg or 100 mg/kg resulted in an increase in preimplantation lethality compared with controls. Total dominant lethality was increased in animals treated with 5 divided doses of 200 mg/kg every 24 hr, 100 mg/kg every 12 hr, or 200 mg/kg every 12 hr. The highest frequency of dominant lethals was found in the group receiving 5 x 200 mg/kg every 12 hr. In general, the incidence of dominant lethals increased with increasing dose levels. Cytologic analysis of chromosome rearrangements in spermatogonia showed that 5 x 200 mg/kg saccharine every 12 hr produced 1.6% translocations and 4.5% separated X and Y chromosomes (univalents).

1864 THE ENZYMIC RELEASE OF O⁶-METHYLGUANINE AND 3-METHYLADENINE FROM DNA REACTED WITH THE CARCINOGEN N-METHYL-N-NITROSOUREA. (E.) Kirtikar, D. M. (Dept. Biochem., Case Western Reserve U., Cleveland, Ohio) and D. A. Goldthwait. *Proc Natl Acad Sci USA* 71(5):2022-2026, 1974.

DNA from bacteriophage T4 (T4 DNA) was reacted with ³H-dimethyl sulfate (DMS) and incubated with endonuclease II (deoxyribonuclease oligonucleotidohydrolase) which had been prepared and purified from *Escherichia coli* JC 4583. This resulted in the release of 3-methyladenine, as detected by isolation of the methylated bases by paper or column chromatography. N-methyl-N-nitrosourea (MNU), in high concentrations, produced many single strand breaks in the DNA molecule; at increasing ratios of MNU:DNA nucleotide, increasing MNU-induced strand breaks were observed. At low ratios of MNU to DNA, there was more alkylation of the O-6 position of guanine relative to the other derivatives than at high ratios. Alkylation of the N-1 and N-7 positions of adenine was also ob-

served. With increasing concentrations of endonuclease II, there were increasing numbers of single-strand breaks. Endonuclease II released O⁶-methylguanine and 3-methyladenine, but not 7-methylguanine, from T4 DNA which had been methylated by MNU; the release of 3-methyladenine occurred at a rate approximately 4 times that of the other bases. The amounts of O⁶-methylguanine and 3-methyladenine released from the alkylated DNA by the enzyme were balanced by the amounts of these bases disappearing from the DNA. The data support the hypothesis that depurination is an intermediate step in phosphodiester bond breakage by endonuclease II. They further indicate that the endonuclease II of *E. coli* represents a new DNA repair system which may be specific for purines.

1865 MOLECULAR AND CELLULAR MECHANISMS ASSOCIATED WITH PULSE-CARCINOGENESIS IN THE RAT NERVOUS SYSTEM BY ETHYLNITROSOUREA: ETHYLATION OF NUCLEIC ACIDS AND ELIMINATION RATES OF ETHYLATED BASES FROM THE DNA OF DIFFERENT TISSUES. (E.) Goth, R. (Max Planck Inst. Virus Res., Tübingen, W. Germany) and M. F. Rajewsky. *Z Krebsforsch* 82(1):37-64, 1974.

The ethylation of nucleic acids by the nervous system-specific pulse-carcinogen, N-ethyl-N-nitrosourea (ENU) was investigated in different tissues of the fetal, 10-day-old, and adult BD IX rats and compared with data on the ethylation of rat liver nucleic acids by the hepatocarcinogen ¹⁴C-1-diethylnitrosamine. One hr after a pulse of ¹⁴C-1-ENU, the molar fractions of N7-ethylguanine (N7-EG), O6-ethylguanine (O6-EG), N3-ethyladenine (N3-EA), and N7-ethyladenine (N7-EA) were similar in the DNA of "high risk" (fetal or 10-day-old brain) and "low risk" tissues (for example, liver), and independent of the fraction of cells engaged in DNA replication at the time of the ENU pulse. While the respective elimination rates from DNA of brain and other tissues were similar for N7-EG and N3-EA, O6-EG was removed from brain DNA much more slowly than from liver DNA or from the DNA of other pooled tissues. The capacity of the target cell to eliminate O6-EG from its DNA, together with the frequency of DNA replication, may be an important factor in determining the probability of neoplastic transformation.

1866 DYNAMIC STRUCTURE OF DNA MODIFIED WITH THE CARCINOGEN N-ACETOXY-N-2-ACETYLAMINOFLUORENE. (E.) Fuchs, R. P. P. (Inst. Molecular Cellular Biol., Strasbourg, France) and M. P. Duane. *Biochemistry* 13(21):4435-4440, 1974.

Native calf-thymus DNA was allowed to react with N-acetoxy-N-2-acetylaminofluorene and the dynamic behavior of this carcinogen-reacted DNA was studied with the formaldehyde unwinding technique. In all cases, the initial rate of formaldehyde attack is higher for DNA reacted with the carcinogen than for native DNA. Thus, in addition to the "natural breathing" of the DNA duplex, each fixed fluorene residue gives rise to weak points from which formaldehyde unwinding starts. A model is proposed that enables one to determine the size of these

disorganized loops at temperatures between 30 and 10° below the melting temperature. Theoretical calculations showed that the destabilizing effect measured by direct helix-coil transition is consistent with the model obtained from pure kinetic data. The possible biological consequences of permanently open sections in native DNA for chemical carcinogenesis are briefly considered.

1867 INDUCTION OF SISTER CHROMATID EXCHANGES BY CHEMICAL MUTAGENS AND ITS POSSIBLE RELEVANCE TO DNA REPAIR. (E.) Kato, H. (Nat'l. Inst. Genetics., Mishima, Japan). *Exp Cell Res* 85(2): 239-247, 1974.

Several chemical mutagens were found to induce sister chromatid exchanges in Chinese hamster chromosomes. The effects of 4-nitroquinoline 1-oxide (4NQO) and mitomycin C (MMC) were similar to those of UV light in that the exchange frequency increased with increasing dosage, being markedly lowered in the presence of 1 mM caffeine during a posttreatment period. The frequency of proflavin-induced sister chromatid exchanges was also dose-dependent, but it was insensitive to the caffeine posttreatment. On the other hand, no appreciable increase was detected in the incidence of sister chromatid exchanges in cells treated with *N*-methyl-*N*-nitro-*N*-nitroso-guanidine over a 100-fold range of variation in dosage. Caffeine alone raised the exchange frequency only slightly over control levels. 4NQO and MMC exerted remarkable delayed effects on the exchange induction, whereas proflavin did not. This suggests that the lesions caused by the former mutagens would be long-lived and should provoke sister chromatid exchanges. The data indicate that there are several possible ways in which the initial DNA lesions ultimately lead to the formation of sister chromatid exchanges, and that at least UV-, 4NQO-, and MMC-induced sister chromatid exchanges evolved through a caffeine-sensitive repair process, probably related to a postreplication repair of DNA damage.

1868 COMPARATIVE STUDIES OF THE EFFECTS OF CARCINOGENIC AND ANTITUMOR AGENTS ON THE DNA REPLICATION OF CULTURED MAMMALIAN CELLS. (E.) Makino, F. (Fac. Med., U. Tokyo, Japan) and S. Okada. *Mutat Res* 23(3):387-394, 1974.

Cultured mouse L5178Y cells were exposed to several carcinogenic and antitumor agents, after which they were labeled with ³H-thymidine for 20 min; the agents were applied at dose levels sufficient to inhibit ³H-thymidine uptake by 30-50%. The DNA was subjected to alkaline sucrose gradient centrifugation immediately or after a chase period, and the DNA replication patterns examined. The carcinogenic and antitumor agents were classified into three groups based on the results. Ultraviolet irradiation, 4-nitroquinoline-1-oxide (4NQO), *N*-methyl-*N*'-nitrosoguanidine (MNNG), nitrogen mustard, and Mitomycin C constituted the first group. These agents resulted in 20-min DNA labeling patterns showing the formation of small DNA; they also slowed down subsequent molecule elongation.

The replicated DNA strands had gaps where "damage" was present on the parental strands. Subsequently, gap-filling replication occurred with or without damage repair. Gamma irradiation was the sole member of the second group. After exposure to it, the 20-min DNA labeling profile demonstrated larger DNA strands, the subsequent elongation of this DNA being slightly affected. This was probably due to a preferential depression of the initiation of DNA replication. The third group consisted of methyl methanesulfonate (MMS) and low temperature (28 C). The 20-min DNA labeling patterns were qualitatively similar to, but quantitatively different from, those of nonirradiated controls. The rate of DNA elongation was slightly retarded.

1869 DNA-PROTEIN COMPLEXES PRODUCED BY A CARCINOGEN, β -PROPIOLACTONE. (E.) Nietert, W. C. (U. Wisconsin Sch. Med., Madison), L. M. Kellicutt and H. Kubinski. *Cancer Res* 34(4):859-864, 1974.

DNA and various proteins formed complexes when exposed *in vitro* to β -propiolactone (BPL, 1% in 0.1 M NaCl-0.02 M phosphate buffer). These artificially produced "nucleoproteins" were detected by their increased sedimentation, decreased mobility in gels during electrophoresis, lowered buoyant density in CsCl and Cs₂SO₄ gradients, and increased retention on methyl-esterified albumin-kieselguhr columns, compared with untreated DNA-protein mixtures and BPL-treated DNA alone. Initially, the complexes are soluble in ionic detergents, but during longer exposure to BPL a transition to an insoluble structure is observed. The chemical nature of the protein-DNA bonds is unknown. Since BPL is a powerful carcinogen, the possibility that the cross-linking of proteins to DNA plays a role in chemical oncogenesis is considered.

1870 EFFECT OF ORAL CONTRACEPTIVES ON THE MAMMARY GLANDS OF RHESUS MONKEYS: A PRELIMINARY REPORT. (E.) Drill, V. A. (Res. Labs., G. D. Searle & Co., Stokie, Ill.) D. P. Martin, E. R. Hart and R. G. McConnell. *J Nat'l Cancer Inst* 52(5):1655-1657, 1974.

The 5 yr effects of oral contraceptives Enovid-E or Ovulen, on the occurrence of mammary lesions in female rhesus monkeys (*Macaca mulatta*) are presented. For each contraceptive studied, 64 conditioned monkeys were divided into 4 groups of 16 animals each. One group served as untreated controls; the other 3 groups were treated with either a low, medium, or high dose of compound. For Enovid-E, doses were 0.05 mg/kg, 0.5 mg/kg, and 2.5 mg/kg. For Ovulen, doses were 0.02 mg/kg, 0.2 mg/kg, and 1.0 mg/kg. Estrogen levels were the same for both Enovid-E and Ovulen: 0.002 mg/kg, 0.02 mg/kg, and 0.1 mg/kg. These doses of contraceptive were 1, 10, and 50 times the average human dose. There were 7 nondrug-related deaths in the study. Palpable nodules were not present in any control, Enovid-E, or Ovulen treated monkeys, as determined by examination of

the mammary glands on days 24-28 of each cycle. When the glands were "milked", most monkeys in the medium- and high-dose groups had a discharge that varied in quantity and quality from slight and watery to full lactation. Mammary glands hypertrophy was uncommon with Enovid-E and showed no relationship to mammary discharge. With Ovulen, lactation was occasionally accompanied by hypertrophy of the gland. The treated animals showed ductal hyperplasia, metaplasia, and acinar dilation, but mammary cancer did not occur.

- 1871 THE TRANSPORT AND LOCALIZATION OF BENZO-(α)PYRENE-HEMATITE AND HEMATITE- ^{210}Po IN THE HAMSTER LUNG FOLLOWING INTRATRACHEAL INSTILLATION. (E.) Kennedy, A. R. (Harvard Sch. Publ. Hlth., Boston, Mass.) and J. B. Little. *Cancer Res* 34(6):1344-1352, 1974.

The localization within the lung of ^{210}Po and benzo-(α)pyrene (BP) adsorbed onto hematite particles was studied following intratracheal instillation into male Syrian golden hamsters. ^{210}Po and BP localization within the lung were studied by freeze-dry autoradiography and UV-fluorescence microscopy, resp. Following a single instillation, ^{210}Po and BP tended to be deposited in a nonhomogeneous manner, ^{210}Po distribution being greater in the basal regions down as far as the bronchiole-alveolar ducts and BP being primarily retained in the upper airway epithelial cells. Multiple instillations resulted in a somewhat more diffuse distribution. ^{210}Po remained associated with the hematite, whereas BP became dissociated and entered the epithelial cells alone. Hematite- ^{210}Po produced combined epidermoid and adenocarcinomas in the peripheral lung, while BP-hematite produced primarily epidermoid carcinomas of the major bronchi and trachea.

- 1872 SOME CONSIDERATIONS OF METAL CONTENT OF TOBACCO PRODUCTS. (E.) Nadkarni, R. A. (Dept. Chem., Cornell U., Ithaca, N.Y.). *Chem Ind* (17):693-696, 1974.

Among the potentially toxic elements present in tobacco are arsenic and selenium. The levels of the former vary from 40-60 ppm to less than 10 ppm, and it is doubtful that cigarette smoke arsenic is a strong carcinogen unless the smoker consumes two or more packages a day. The levels of selenium vary from 0.14-5.8 ppm in cigarette tobacco and 1.1-5.5 ppm in cigarette paper; levels of about 2.5 ppm are found in pipe and cigar tobacco. Other elements which have been found in trace amounts in tobacco are aluminum, beryllium, bromine, cadmium, chromium, calcium, cobalt, copper, gold, iron, magnesium, manganese, mercury, molybdenum, nickel, sodium, thallium, titanium, and zinc. Many of these elements are also found in cigarette paper, the levels varying with brand. Potassium, sodium, lead, arsenic, calcium, magnesium, aluminum, iron, manganese, copper, mercury, chromium, cadmium, nickel, and zinc are found in substantial amounts in cigarette smoke, the latter two also being found in appreciable quantities

in sidestream smoke. A standard reference cigarette has been made and distributed by the University of Kentucky Tobacco and Health Research Institute to serve as a basis of inter- and intra-laboratory comparative studies. The trace element composition of this cigarette tobacco and the smoke condensate is summarized, as is the percent transfer of trace elements into the smoke condensate. Further work is needed to characterize the chemical composition of tobacco and tobacco smoke and to elucidate their relationship with health problems if any.

- 1873 INTERACTION OF CHEMICAL CARCINOGENS WITH PLASMA MEMBRANES: THE EFFECT OF DIMETHYL-AMINOAZOBENZENE ON ERYTHROCYTE OSMOTIC FRAGILITY. (E.) Litman, G. W. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.) and R. J. Litman. *Biochem Biophys Res Comm* 60(2):865-871, 1974.

The ability of the hepatocarcinogen dimethylaminoazobenzene (DAB), and two of its analogs (3'-Me-DAB and 2-Me-DAB) to protect human erythrocytes against osmotic lysis was studied *in vitro*. DAB ($<10^{-5}$) over a 25-fold range protected human RBC against lysis by 0.36-0.40 g % NaCl. The protective effect of DAB was greater than that of 9 steroids previously shown to have antihemolytic effect. At higher concentrations, DAB showed a direct lytic effect on human RBC. Two DAB analogs, one more carcinogenic (3'-Me-DAB) and the other noncarcinogenic (2'-Me-DAB), were even more effective in protecting human RBC from lysis. These results suggest that the methyl derivatives more effectively partition themselves to the RBC membrane than does DAB.

- 1874 IMMUNO-HISTOCHEMICAL STUDY OF BRAIN SPECIFIC S-100 PROTEIN EXPERIMENTAL BRAIN TUMORS. (Ger.) Stavrou, D. (Inst. Pathol. Neuro-pathol., U. Munich, W. Germany), K. G. Haglid, H. Zankl and K. D. Zang. *Z Krebsforsch* 82(1):75-82, 1974.

In 50 adult Sprague-Dawley rats 42 neurogenic tumors were induced by 5 mg/kg *N*-methyl-*N*-nitrosourea in the drinking water. Out of this series, 12 brain tumors were prepared for *in vitro* culture. Cytological tests were performed on the primary tumors as well as on the cultures to determine the brain specific S-100 protein by indirect immunofluorescence. In 10 of 12 brain tumors tested a specific fluorescence exclusively localized in the cytoplasm could be observed. In two pleomorphic brain tumors the existence of S-100 protein could not be traced in either frozen sections or in culture. The cultures of tumors containing S-100 protein were of mixed type. Cells with specific as well as non-specific fluorescence grew side by side. Even after a number of *in vitro* passages the cells showing the specific fluorescence did not change their characteristic fluorescent nature. From these findings it is concluded that the immuno-histochemical test is an effective method to characterize the glial cells by determining brain specific proteins.

- 1875 POSSIBLE ROLE OF MUCOSAL DAMAGE IN STOMACH CARCINOGENESIS WITH N-METHYL-N'-NITRO-N-NITROSOGUANIDINE IN THE RAT. (E.) Tabuchi, Y. (Kobe U. Sch. Med., Japan), T. Ogino, T. Mitsuno and T. Sugiyama. *J Natl Cancer Inst* 52(5):1589-1594, 1974.

Cytopathic and carcinogenic effect of intermittent pulse intragastric administration of a saturated solution (5 mg/ml) of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) on the Wistar rat stomach were studied. The rats received 30 mg MNNG/wk (total 540-600 mg/rat). Degenerative changes in the surface epithelium of the glandular stomach and the forestomach were found 1 hr after the intragastric infusion of 2 ml MNNG solution. Deeper cells were also affected and complete erosion was formed in every rat on day 4 after three successive doses. The epithelium was then allowed to regenerate by cessation of MNNG administration for the following 4 days. Continuation of the weekly damage-and-repair process rapidly produced gastric cancers. The cancers were in the same mucosal regions where erosion was preferentially formed. The results suggest a role of mucosal damage and its repair in gastric carcinogenesis.

- 1876 EFFECT OF THE HEPATOCARCINOGEN ETHIONINE ON HEPATIC STEROID SYNTHESIS. (E.) Hancock, R. L. (Jackson Lab., Bar Harbor, Maine) and A. A. Kandutsch. *Physiol Chem Physiol* 6(3):239-244, 1974.

Experiments were carried out to ascertain whether the rate of hepatic sterol synthesis or the system for feedback regulation of the sterol synthesis pathway is changed by the hepatocarcinogen ethionine. The rate of hepatic sterol synthesis from acetate and the level of 3-hydroxy-3-methylglutaryl Coenzyme A reductase activity in nonneoplastic liver tissue were elevated in C57BL/6J mice fed 0.5% ethionine for prolonged periods of time (up to 365 days). Rates of sterol synthesis reached levels as high as 15 times normal. The rate of sterol synthesis was reduced 85% in non-neoplastic liver tissue by the addition of cholesterol to the diets of mice fed ethionine for 225 days. Thus, feedback response to cholesterol was normal.

- 1877 EFFECT OF N-(3,5-DICHLOROPHENYL)SUCINIMIDE ON THE HISTOLOGICAL PATTERN AND INCIDENCE OF KIDNEY TUMORS IN RATS INDUCED BY DIMETHYLNITROSOAMINE. (E.) Ito, N. (Nara Med. U., Japan), S. Sugihara, S. Makiura, M. Arai, K. Hirao, A. Denda and O. Nishio. *Gann* 65(2):131-138, 1974.

Post-treatment of male Wistar rats with N-(3,5-dichlorophenyl)succinimide (5000 ppm added to diet) markedly increased the induction of tumors, especially renal cells tumors, by dimethylnitrosamine (500 ppm added to diet), but pretreatment with this substance clearly inhibited the induction of tumors, especially embryonal cell tumors in the kidney. Administration of N-(3,5-dichlorophenyl)succinimide alone caused severe interstitial nephritis but not development of kidney tumors. Thus, treatment with N-(3,5-dichlorophenyl)succinimide changes the histo-

logical type and incidence of kidney tumors in rats induced by dimethylnitrosamine. The reason for this is unknown but it is postulated that changes in the tubular epithelium induced by dimethylnitrosamine might be accelerated by the administration of N-(3,5-dichlorophenyl)succinimide, but pretreatment with N-(3,5-dichlorophenyl)succinimide showed results the reverse of those caused by a post-treatment with the nephrotoxic chemical. Thus it changed the susceptibility of epithelial and mesenchymal cell elements of the kidney to induction of tumors of dimethylnitrosamine.

- 1878 PRESENCE OF A-TYPE AND ABSENCE OF C-TYPE VIRUS PARTICLES IN A CHEMICALLY INDUCED GUINEA PIG HEPATOMA. (E.) Dunkel, V. C. (Natl. Cancer Inst., Bethesda, Md.), R. C. Bast, Jr., B. I. Gerwin, U. Heine, M. Cottler-Fox and T. Borsos. *J Natl Cancer Inst* 53(2):591-593, 1974.

C-type virus particles and reverse transcriptase activity could not be detected in cells from a diethylnitrosamine-induced guinea pig hepatoma after treatment with 5-bromo-2'-deoxyuridine (5-BUDR, 2.5-160 µg) or 5-iodo-2'-deoxyuridine (40 µg) in cell culture. A-type particles were found in the presence or absence of 5-BUDR.

- 1879 EFFECT OF N-METHYL-N-NITROSOUREA ON THE PROTEIN-SYNTHESIZING SYSTEM IN MOUSE LIVER AND HEPATOMA 22a CELLS. (E.) Abakumova, O. Y. (Acad. Med. Sci., Moscow, USSR), T. Y. Ugarova, L. B. Gorbacheva, N. G. Kucenco, N. N. Pilipenco, I. S. Sokolva and M. I. Lerman. *Cancer Res* 34(7):1542-1547, 1974.

A single injection of nitrosomethylurea (80 mg/kg i.p.) to mice bearing hepatoma 22a led to an injury of the main components of the protein-synthesizing system (polyribosomal complex and soluble factors of the cell sap) in liver and hepatoma cells. In liver cells of adult animals, the activity of the protein-synthesizing system returns to a normal level 5 to 15 hr after injection, while in hepatoma the process is irreversible for at least 48 hr. These results were confirmed and extended in experiments conducted *in vitro* with cell-free protein-synthesizing systems.

- 1880 DEVIATION IN ESTERASE ISOENZYME PATTERN DURING EARLY STAGE OF HEPATOCARCINOGENESIS BY 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE. (E.) Kaneko, A. (Sapporo Med. Coll., Japan), K. Dempo, Y. Yoshida, N. Chisaka and T. Onoe. *Cancer Res* 34(8):1816-1821, 1974.

With 2-naphthyl acetate as substrate, the activity and isoenzyme pattern of the nonspecific esterase were examined in the microsomal fractions of liver homogenates from male Wistar rats fed a diet containing 0.06% 3-methyl-4-dimethylaminoazobenzene (3'-Me-DAB). Essentially no differences in total esterase activity was found between normal livers and livers of rats fed 3'-Me-DAB for 6 weeks, even

though hepatocyte degeneration with decreased glucose-6-phosphatase activity was evident at this time. During this precancerous stage, however, electrophoretic studies indicated a shift in the hepatic isoenzyme pattern which was attributed to hepatocyte alteration during azo dye feeding. This altered pattern resembled that seen in infant liver, regenerating liver, and in noncancerous areas of tumor-bearing liver. The esterase pattern from hepatomas deviated more from the normal adult liver type than did precancerous liver, revealing a fetal-type esterase with cholinesterase activity that was much greater than that found in normal fetal and adult livers.

- 1881 THE EFFECT OF METABOLIC ACTIVATION WITH RAT LIVER PREPARATIONS ON THE MUTAGENICITY OF SEVERAL N-NITROSAMINES ON A STREPTOMYCIN-DEPENDENT STRAIN OF *ESCHERICHIA COLI*. (E.) Nakajima, T. (Nat'l. Inst. Hyg. Sci., Tokyo, Japan), A. Tanaka and K.-I. Tojyo. *Mutat Res* 26(5):361-366, 1974.

The mutagenicity of dimethyl, diethyl, di-*n*-propyl, di-*n*-butyl, methyl-*n*-butyl, morpholine, piperidine, methylphenyl, ethyl-*t*-butyl, and diphenyl nitrosamines was investigated with a mammalian metabolic activation system. Reverse mutation from streptomycin dependence to nondependence in strain Sd-B(TC) of *Escherichia coli* was used as the marker for mutagenicity. With this assay system the mutagenicity of metabolic breakdown products was determined by incubating the compounds with a rat liver preparation in the presence of bacterial cells. Reverse mutation was induced by all carcinogenic compounds tested, except methylphenylnitrosamine, whereas two noncarcinogenic compounds, ethyl-*t*-butyl nitrosamine and diphenyl nitrosamine, did not give a significant increase in the reversion frequency. The low mutagenicity of methylphenylnitrosamine in this system may be related to the fact that this compound induces tumors in the esophagus but not in the liver; and thus its metabolic activation may be organ-specific.

- 1882 THE EFFECT OF HYPERTONIC SALINE ON THE UPTAKE OF TRITIATED 7,12-DIMETHYLBENZ(A)ANTHRACENE BY THE GASTRIC MUCOSA. (E.) Capoferro, R. (Rikshosp., Oslo, Norway) and O. Torgersen. *Scand J Gastroenterol* 9(4):343-349, 1974.

Stomachs of pylorus-ligated rats and guinea-pigs were rinsed with 0.15 M or 2 M saline before and 2 hr after intragastric instillation of tritiated 7,12-dimethylbenz(a)anthracene (DMBA). The uptake of radioactivity by the gastric wall was measured by liquid scintillation counting. In rats, the radioactivity of the forestomach was more than 10 times higher than that of the glandular stomach. In both rats and guinea-pigs, the radioactivity tended to decrease from the fundus to the antrum. Rinsing the stomach with 2 M saline 2 hr after ³H-DMBA instillation reduced the *p*-aminosalicylic acid-stained mucus as well as the radioactivity of the gastric wall. This may indicate that gastric mucus binds DMBA and that hypertonic saline washes the mucus away. Rinsing the

stomach with 2 M saline before instillation of ³H-DMBA caused an increased uptake. This observation may be significant regarding the pathogenesis of stomach cancer, as earlier epidemiologic studies indicated that a high consumption of salted food in populations with high incidence of this disease.

- 1883 INHIBITORY EFFECTS OF NITROSOSARCOSINE ON MOUSE LIVER MIXED FUNCTION OXIDASE ACTIVITY. (E.) Friedman, M. A. (Med. Coll. Virginia, Richmond). *Experientia* 30(8):857-859, 1974.

Male Swiss ICR/dub mice were inoculated p.o. with 0, 250, 500, or 1000 mg/kg nitrososarcosine, and the dose response of liver aminopyrine demethylase and aniline hydroxylase determined 45 min later. The time course of the response was measured 0, 0.25, 1, 3, and 24 hr after p.o. administration of 1000 mg/kg nitrososarcosine. The liver aminopyrine demethylase and aniline hydroxylase activities were inhibited 59% and 62%, respectively by 1000 mg/kg nitrososarcosine and 27% and 18% by 250 mg/kg nitrososarcosine. Maximum inhibition of microsomal enzyme activity occurred about one-three hr after treatment. Nitrososarcosine competitively inhibited aminopyrine demethylase activity. The doses of nitrososarcosine necessary to induce this effect were 10-fold lower than the toxic doses for this compound. To determine whether these effects were unique to nitrososarcosine, dimethylnitrosamine and dibutylnitrosamine were tested under similar conditions. The former induced no inhibition of aminopyrine demethylase activity within three hr, while the latter induced little inhibition.

- 1884 RIBOSOME FRACTIONS FROM NORMAL AND METHYLCHOLANTHRENE-TREATED MOUSE EPIDERMIS. (E.) Argyris, T. S. (Upstate Med. Ctr., Syracuse, N.Y.), C. Nevar, S. Mueller, L. de Young and G. Gordon. *J Invest Dermatol* 63(3):262-267, 1974.

Ribosome fractions were isolated from normal trypsinized epidermis of female CD-1 mouse skin and from skin to which 2 μM 3-methylcholanthrene (3MC) in benzene solution had been applied. Almost all of the ribosomal RNA in the normal epidermis was recovered in the postmitochondrial fraction, very little being found in the nuclear and mitochondrial fractions. Most of the ribosomes were free (83%), about 17% being membrane bound. Four days after treatment of epidermis in the resting phase of the hair growth cycle with 3MC, the epidermis was considerably thickened. There was a significant increase in the total amount of ribosomal RNA/gm of epidermis; the increases in free and membrane-bound ribosomes were proportional. Again, almost all of the ribosomes were found in the postmitochondrial supernatant fraction. The normal epidermis contained mostly monosomes and some subunits, while in the 3MC-treated epidermis, dimers appeared separate from the polysome area. In the former case, RNase pretreatment did not change the gradient profile significantly, while in the latter case, RNase pretreatment resulted in a definite decrease in dimers and an increase in monosomes.

- 1885 A STUDY OF THE DOSE RESPONSE OF MOUSE SKIN TO CIGARETTE SMOKE CONDENSATE. (E.) Davies, R. F. (Tobacco Res. Council Lab., Harrogate, England), P. N. Lee and K. Rothwell. *Br J Cancer* 30(2):146-156, 1974.

Smoke condensate from two types of cigarette, dissolved in two solvents, was applied regularly to the backs of mice at each of seven different dose levels (65-300 mg/wk). Treatment was continued three times/wk for up to 110 wk, by which time 509 of the 1428 treated mice had developed skin tumors, including infiltrating carcinoma. The dependence of tumor incidence on age was adequately described by the Weibull distribution. The relationship between dose of smoke condensate and tumor incidence rate was, however, erratic. It was less regular than the simple relationship which has been obtained when the pure carcinogen benzo(a)pyrene is applied to mouse skin. The best dose levels for comparative testing of the carcinogenicity of cigarette smoke condensates are 90-180 mg/wk.

- 1886 RESISTANCE TO SKIN TUMORIGENESIS BY 3-METHYLCHOLANTHRENE IN MICE SUSCEPTIBLE TO LEUKEMIA. (E.) Duran-Reynolds, M. L. (Albert Einstein Coll. Med., Bronx, N.Y.) and C. Cook. *J Natl Cancer Inst* 52(3):1001-1003, 1974.

RF/J female mice were tested for their response to skin painting with 1% 3-methylcholanthrene (MCA) in benzene, with and without vaccinia virus infection. The experimental group received 1 mg cortisone s.c. daily for 5 days, followed by vaccinia inoculated intradermally, and MCA painting once a day for 5 days. Three control groups received: 1) cortisone, heat-inactivated vaccinia, and MCA; 2) live vaccinia and MCA; and 3) MCA. Although the four groups developed 90-95% leukemia, only the experimental group also developed skin tumors (82%) at the site of the acute skin lesions induced by vaccinia. These results confirm previous observations in different inbred mice, which indicated that MCA painting induces few or no skin tumors in mice having a significantly high incidence of leukemia.

- 1887 ON THE BIOCHEMICAL MECHANISM OF TUMORIGENESIS IN MOUSE SKIN. V. STUDIES OF THE METABOLISM OF TUMOR PROMOTING AND NONPROMOTING PHORBOL DERIVATIVES *IN VIVO* AND *IN VITRO*. (E.) Kreibich, G. (German Cancer Res. Ctr., Heidelberg, W. Germany), R. Süss and V. Kinzel. *Z Krebsforsch* 81(2):135-149, 1974.

The metabolism of radiolabeled tumor-promoting phorbol esters, 12-*O*-tetradecanoyl-phorbol-13-acetate (TPA) and phorbol-12,13-didecanoate (PDD), and of the inactive epimer of PDD, 4 α -phorbol-12,13-didecanoate (4 α -PDD), was studied 12 hrs after their topical application to the back skin of adult NMRI mice. The results were compared with those obtained after the *in vitro* incubation of the labeled phorbol derivatives with embryonic mouse skin and with cultures of HeLa and L-cells. PDD, 4 α -PDD, and TPA were poorly

metabolized *in vivo* after 12 hrs. In monolayer and suspension cultures of HeLa cells, where at very low concentrations (10^{-8} M) only phorbol esters with tumor-promoting activity *in vivo* block DNA synthesis and stimulate the incorporation of choline into lipids, hardly any metabolic changes were observed in the biologically active or inactive phorbol derivatives. In monolayer and suspension cultures of L-cells, all phorbol derivatives tested were metabolized to a considerable extent within 12 hr; this correlates with the lack of response in blocking DNA synthesis and stimulation of lipid turnover. The data suggest that tumor-promoting phorbol esters need no metabolic activation.

- 1888 ON THE BIOCHEMICAL MECHANISM OF TUMORIGENESIS IN MOUSE SKIN. VI. EARLY EFFECTS OF GROWTH-STIMULATING PHORBOL ESTERS ON PHOSPHATE TRANSPORT AND PHOSPHOLIPID SYNTHESIS IN MOUSE EPIDERMIS. (E.) Balmain, A. (German Ctr. Cancer Res., Heidelberg, W. Germany) and E. Hecker. *Biochim Biophys Acta* 362(3):457-468, 1974.

The effect of the tumor promotor 12-*O*-tetradecanoyl-phorbol-13-acetate (0.02 μ M) on 32 P-labeled orthophosphate (32 P_i) incorporation into the phosphatidylcholine fraction in female NMRI mouse epidermis was investigated. Two peaks in incorporation were observed, one at 4-6 hr and at 48 hr after treatment. The incorporation of 3 H-thymidine into the DNA of mouse epidermis was inhibited for about 10 hr after administration of 12-*O*-tetradecanoyl-phorbol-13-acetate. At the same time, the incorporation of 32 P_i into epidermal DNA was rapidly stimulated, suggesting that the specific activity of the intracellular ATP pool is increased by the tumor promotor soon after its application. The first peak in 32 P_i incorporation into phosphatidylcholine may be attributed in part to pool changes. Isolated pieces of mouse skin pretreated with 12-*O*-tetradecanoyl-phorbol-13-acetate were capable of incorporating 32 P_i into the phosphatidylcholine fraction in a manner which is similar to that observed *in vivo*. The early accumulation of phosphatidylcholine within the epidermis is, therefore, due to the localized stimulation of the skin microsomal enzymes responsible for its synthesis.

- 1889 INFLUENCE OF ORAL CONTRACEPTION ON CYTOLOGY AND HISTOLOGY OF THE CERVIX UTERI: POPULATION SCREENING FOR CERVICAL CARCINOMA IN MARIBO AMT 1967-1969. (E.) Berget, A. (Central Hosp., Nykøbing Falster, Denmark) and T. Weber. *Dan Med Bull* 21(5):172-176, 1974.

Between 1967 and 1969, 13,125 women aged 30-50 yr were screened by PAP smear to determine the influence of oral contraception with estrogen-progesterone-containing birth control (BC) pills on cytology of the uterine cervix. The incidence of abnormal cytologic findings obtained in 446 women showed no difference between those using BC pills and those using other forms of contraception. Histologic examination revealed 69 patients with dysplasia.

Of the 446 women, 236 had carcinoma *in situ* and 45 had invasive carcinoma. The remaining 96 women showed nonspecific infection, hyperplasia, or no pathologic change. Further analysis of the 446 women with abnormal cytologic findings and of the subgroup of 236 with *in situ* carcinoma showed no difference between BC pill users and users of other forms of contraception with respect to age, number of pregnancies, and age at first pregnancy. No difference in incidence was observed with respect to socioeconomic status except for prestige class 6 (middle class) where abnormal cytologic findings occurred in 4.9% of BC pill users *versus* 2.8% of nonusers ($P < 0.02$).

- 1890 HORMONE BALANCE AND APPLICATION OF COSMETICS CONTAINING HORMONES. (E.) Everse, J. W. R. (Organon Internatl. B.V., Oss, Holland). *Cosmetics Perfumery* 89(9):90-94, 1974.

This discussion on hormones in cosmetics relates to the sex hormones, estrogenic and progestational substances, and compares the amounts absorbed through the application of cosmetics with the amount produced naturally. When the maximum amount of estrogen that might be absorbed through the skin is compared to the amount produced naturally, it is seen to be 5 to 10% of the average daily production. When the quantity of the synthetic hormone, ethisterone, contained in a hormone cream (0.4 mg/g cosmetic) is compared with natural progesterone production, it is estimated that the amount absorbed would increase the daily progestational effect of natural production by 0.2-1.25% at most, a value lying within the physiological range of variation of progesterone production. Since the quantities absorbed from estrogen cosmetics in normal use are certainly within the range of variation of the physiological concentration, the risk of carcinogenic effect is purely theoretical. No carcinogenic effect on the skin itself has ever been observed. As far as the progestogens are concerned, it is known that they have a favorable effect on certain carcinomas, for example uterine and cervical carcinoma.

- 1891 EXPERIMENTAL ALTERATION OF THE PHENOTYPE OF ANIMAL CELLS *IN VIVO*. (E.) Huggins, C. B. (Ben May Lab. Cancer Res., U. Chicago, Ill.). *J Clin Pathol* 27(7):1-3, 1974.

Three simple methods for experimentally transforming normal cells into normal cells of another type in adult animals and for changing, rapidly and invariably, the program of normal cells into neoplasms are presented. There are two methods for altering the phenotype of competent fibroblasts. These consist of bringing them into association with transforming epithelium or demineralized matrices of bone and tooth. Approximation of the transformant and responding fibroblast initiates a series of interconnected biochemical reactions which yield highly distinctive products. The net result is permanent

alteration of the phenotype of the fibroblast, responding fibroblasts brought into contact with transforming epithelium change to osteoblasts, while responding fibroblasts brought into contact with matrices of bone or tooth change to chondroblasts. Regarding the transformation of normal cells into neoplasms, stem cells of the reticuloendothelial system change to erythroblastic leukemia after exposure to highly active polycyclic aromatic hydrocarbons.

- 1892 CONVERSION OF 3 β -HYDROXY-PREGN-5-EN-20-ONE TO PROGESTERONE BY TRANSPLANTABLE CHORIO-CARCINOMA IN RATS. (E.) Miyamoto, M. (Osaka U. Med. Sch., Japan), T. Sugaya and K. Matsumoto. *J Natl Cancer Inst* 52(4):1359-1360, 1974.

A transplantable tumor was induced by 7,12-dimethylbenz(a)anthracene in the uterus of a rat from which a fetus had been removed. Some rat tissues were incubated with ^{14}C -3 β -hydroxypregn-5-en-20-one in organ culture. ^{14}C -progesterone was formed in the tumor and placenta as well as in the cultures of testes, ovaries, and adrenals, but none (or little) could be found in the liver, spleen, kidney, and muscle cultures. In addition, radioactive testosterone, 20 α -hydroxypregn-4-en-3-one, and corticosterone were formed by the testes, ovaries, and adrenals in culture, respectively. The data support the morphologic finding that the tumor seemed to be derived from chorionic cells.

- 1893 ACTIVITY AND HORMONE RESPONSIVENESS OF ADENYL CYCLASE DURING INDUCTION OF TUMORS IN RAT LIVER WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE. (E.) Boyd, H. (Austin Hosp., Victoria, Australia), C. J. Louis and T. J. Martin. *Cancer Res* 34(7):1720-1725, 1974.

Basal activity and responsiveness to isoproterenol, glucagon, and fluoride of the adenylyl cyclase in the 100 X g fraction of liver homogenates was studied in male Sprague-Dawley albino rats fed a diet containing 0.06% 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) for 12 wk. Six of 11 rats fed the diet developed tumors of various histologic types between 13-28 wk after the start of the experiment. By 2 wk after starting the diet, incorporation of ^3H -ATP into cyclic-AMP in the assay system was stimulated 17% by isoproterenol (5×10^{-4} M) compared to that of controls. Isoproterenol responsiveness, which could be blocked by propranolol, reached a maximum of 480% after 9 wk, during the "precancerous" phase. The glucagon (5×10^{-6} M) responsiveness of adenylyl cyclase remained decreased throughout the entire period. Fluoride response was unchanged. After appearance of tumors (after 12 wk) isoproterenol response decreased but did not fall below control levels. Basal activity, which had risen 270% during the "precancerous" phase, as well as fluoride response fell below control levels; glucagon response remained depressed. Hormone responsiveness of established isolated tumors was variable but never high and basal activity was low.

- 1894 THE ROLE OF THE OVARY IN ESTROGEN PRODUCTION OF MAMMARY CANCER IN THE RAT. (E.) Segaloff, A. (Alton Ochsner Med. Fdn., New Orleans, La.) *Cancer Res* 34(10):2708-2710, 1974.

The role of the ovary in the production of mammary tumors was investigated in five groups each of 42 female A X C rats. All groups were hysterectomized and the ovaries in three of the groups removed at the time of hysterectomy. Four of the experimental groups received a diethylstilbestrol-cholesterol pellet s.c. which remained in place until the animal died or was sacrificed. There was a substantial delay in the onset of the first tumors in all three groups without ovaries and a much smaller number of tumors was seen in these groups. The data presented in this study suggest that the ovary plays an important role in the diethylstilbestrol production of mammary cancer in the A X C rat, the presence of the ovary being required for the highest tumor incidence at the earliest time. The results further suggest that progesterone is probably not the missing element when the ovaries are removed, because neither the continuous nor cyclic administration of progesterone together with diethylstilbestrol is capable of replacing the ovarian effect.

- 1895 INHIBITORY EFFECT OF MANGANESE UPON MUSCLE TUMORIGENESIS BY NICKEL SUBSULFIDE. (E.) Sunderman, F. W. (U. Connecticut Sch. Med., Farmington), T. J. Lau and L. J. Cralley. *Cancer Res* 34(1): 92-95, 1974.

Fischer rats in five experimental groups were given a single i.m. injection of penicillin suspension containing carcinogenic Ni_3S_2 dust (2.5 mg), alone or in combination with equimolar amounts of aluminum, copper, chromium, or manganese dusts. Rats in five control groups were treated identically, except that the Ni_3S_2 dust was omitted. After 24 months, the incidence of sarcomas at the injection site was 63% in the group that received the combination of Ni_3S_2 and manganese dusts, compared with incidences of 96-100% in the groups that received Ni_3S_2 alone or in combination with aluminum, copper, or chromium dusts ($p < 0.001$). No sarcomas occurred at the injection site in control groups that did not receive Ni_3S_2 . The finding that the addition of equimolar amounts of manganese dust to Ni_3S_2 dust significantly depresses Ni_3S_2 -induced tumorigenesis provides an experimental system for investigations of metal interactions in carcinogenesis.

- 1896 INDUCTION OF MICROSOMAL BENZO(a)PYRENE HYDROXYLATION IN LIVER CELL CULTURE BY A SUPEROXIDE-GENERATING SYSTEM. (E.) Paine, A. J. (U. Coll. Hosp. Med. Sch., London, England) and A. E. M. McLean. *Biochem Soc Trans* 2(4):605-606, 1974.

Previous studies have shown that synthesis of aryl hydrocarbon hydroxylase is induced by polycyclic hydrocarbons and certain drugs such as phenobarbital and adrenaline. The stimulation by adrenaline is due to its autooxidation to adrenochrome, probably

mediated by the superoxide ion (O_2^-). The present study investigated the ability of O_2^- alone to stimulate hydrocarbon hydroxylase activity in rat liver epithelial cells grown *in vitro* in the presence of an O_2^- generating system (riboflavin and methionine plus light). Such a system induced enzyme activity to the same extent as did 1,2-benz(a)anthracene and caused no cellular injury. Stimulation of hydroxylase activity was inhibited by cycloheximide. It was thus concluded that O_2^- was the factor common to the stimulation of aryl hydrocarbon hydroxylase activity by both polycyclic hydrocarbons and adrenaline.

- 1897 THE DETECTION AND DETERMINATION OF POLYNUCLEAR AROMATIC HYDROCARBONS BY LUMINESCENCE SPECTROMETRY UTILISING THE SHPOL'SKII EFFECT AT 77K. (E.) Kirkbright, G. F. (Chem. Dept., Imperial Coll., London, England) and C. G. de Lima. *Analyst* 99(1179): 338-354, 1974.

The luminescence emission spectra of 23 polynuclear aromatic hydrocarbons (PAH) were examined in n-alkane solvents at 77 K. The shpol'skii effect, in which narrow-band (quasi-linear) emission spectra are obtained under these conditions when a monochromator of adequate resolving power is used, was readily observed for 12 of the 23 compounds examined in these solvents. Quasi-linear emission spectra were also obtained in tetrahydrofuran for some of the PAH compounds examined. These emission spectra provide for unambiguous qualitative identification of PAH compounds at trace concentrations in solution. At present, the application of this fingerprinting technique is limited to those aromatic hydrocarbons which are soluble in n-alkanes. The ability to obtain quasi-linear emission spectra in tetrahydrofuran, however, suggests that the technique may be extended to compounds that are not soluble in these solvents and that are more polar than PAH compounds.

- 1898 VINYL CHLORIDE: TIME BOMB ON THE PRODUCTION LINE. (E.) Schanche, D. A. (No affiliation). *Today's Health* 52(9):16-19; 70-72, 1974.

The dangers of vinyl chloride, which are beginning to be uncovered as a result of the deaths from angiosarcoma of the liver of at least 20 American and foreign vinyl chloride workers are reviewed together with measures being taken by various companies and government agencies to limit exposure to this carcinogenic gas. All of the occupationally related deaths occurred in men who had long-term exposure (from 12-20 yr) to extremely high concentrations of vinyl chloride. The deaths from angiosarcoma of three women in the Buffalo-Niagara Falls area have also been attributed to vinyl chloride in the air, apparently caused by pollution from a nearby Goodyear Rubber factory. An emergency exposure level of 50 ppm has been set by the government. The National Institute for Occupational Safety and Health has urged the labor department to reduce its vinyl chloride emergency standard permanently to "no detectable level".

1899 SELECTIVE DISTRIBUTION OF THE RADIOACTIVITY IN NERVE TISSUES OF THE MOUSE AFTER INTRAVENOUS ADMINISTRATION OF ^{14}C -LABELED N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Takahashi, G. (Chest Dis. Res. Inst., Kyoto U., Japan). *Gann* 65 (4):363-365, 1974.

The distribution and time course of disappearance of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in mice were determined by macroautoradiography and radiometry. A solution of 10 μC MNNG [*methyl*- ^{14}C] (5.4 Mc/mmol) or MNNG [*guanidino*- ^{14}C] (5.45 mC/mmol) dissolved in water was either injected i.v. or given by gastric intubation to adult or pregnant mice on the 18th day of pregnancy. These mice were sacrificed one or five hr after the administration. When either of the labeled MNNGs was given by either route, radioactivity was distributed uniformly in various organs and fetuses, with a few exceptions. The urinary bladder and gallbladder showed strong radioactivity, suggesting that MNNG would be excreted into the urine and bile. The radioactive intensity was very marked in nerve tissues of adult mice 1 hr after i.v. administration but not so 5 hr later. Gastric intubation failed to demonstrate such density in nerve tissues of adult mice at any time. These findings suggest that MNNG is metabolized so rapidly *in vivo* that induction of tumors in remote organs is unlikely. The rapid distribution of radioactivity derived from ^{14}C -MNNG in nerve tissues may lead to the induction of tumors in these organs, when this chemical is administered i.v.

1900 SELECTIVE PROTECTION OF DIBENAMINE AGAINST DIETHYLNITROSAMINE-INDUCED LIVER BUT NOT OTHER TUMORS. (E.) Weisburger, E. K. (Natl. Cancer Inst., Bethesda, Md.), J. M. Ward and C. A. Brown. *Proc Am Assoc Cancer Res* 15(March):4, 1974.

1901 ULTRASTRUCTURE OF ATYPICAL NODULES IN RAT PANCREAS INDUCED BY 4-HYDROXYAMINOLINE-1-OXIDE. (E.) Shinozuka, H. (Temple U. Sch. Med., Philadelphia, Pa.), J. A. Popp and Y. Konishi. *Proc Am Assoc Cancer Res* 15(March):5, 1974.

1902 A COMPARISON OF CHRYSOTILE AND TRIDYMITTE AT THE INTRATHORACIC SITE IN MALE MARSH MICE. (E.) Bryson, G. (Cottage Hosp. Res. Inst., Santa Barbara, Calif.), F. Bischoff and R. D. Stauffer. *Proc Am Assoc Cancer Res* 15(March):6, 1974.

1903 CHOLESTEROL ALPHA OXIDE TURNOVER AT THE SUBCUTANEOUS INJECTION SITE IN MICE. (E.) Bischoff, F. (Cottage Hosp. Res. Inst., Santa Barbara, Calif.) and G. Bryson. *Proc Am Assoc Cancer Res* 15(March):6, 1974.

1904 THE EFFECTS OF 12-O-TETRADECANOYL-PHORBOL-13-ACETATE (TPA) ON MOUSE EPIDERMAL HISTIDASE ACTIVITY. (E.) Colburn, N. H. (U. Michigan Med. Sch., Ann Arbor) and S. Lau. *Proc Am Assoc Cancer Res* 15(March):10, 1974.

1905 ENHANCEMENT OF SKIN TUMOR INITIATION BY A SINGLE CROTON OIL TREATMENT SOON AFTER INITIATOR APPLICATION. (E.) Hennings, H. (Natl. Inst. Hlth., Bethesda, Md.), D. Michael and E. Patterson. *Proc Am Assoc Cancer Res* 15(March):10, 1974.

1906 ISOTOPE EFFECT ON THE CARCINOGENICITY OF 3-METHYLCHOLANTHRENE BY SELECTIVE DEUTERIATION OF THE 1-METHYLENE GROUP. (E.) Cavalieri, E. (Eppley Inst. Res. Cancer, U. Nebraska, Omaha) and H. Garcia. *Proc Am Assoc Cancer Res* 15(March):14, 1974.

1907 ENZYMATIC DEACETYLATION OF CARCINOGENIC ARYLACETAMIDES BY DOG LIVER MICROSOMES. (E.) Lower, Jr., G. M. (U. Wisconsin Med. Sch., Madison) and G. T. Bryan. *Proc Am Assoc Cancer Res* 15(March):14, 1974.

1908 CELL CYCLE-DEPENDENT REJOINING OF SINGLE STRAND BREAKS IN TRANSFORMABLE MOUSE FIBROBLASTS TREATED WITH N-METHYL-N'-NITRO-N-NITROSOGUANIDINE. (E.) Peterson, A. R. (McArdle Lab., U. Wisconsin, Madison), J. S. Bertram and C. Heidelberger. *Proc Am Assoc Cancer Res* 15(March):15, 1974.

1909 AFLATOXIN B_1 (AFB_1) DOES NOT PROLONG HEPATIC DNA REPAIR. (E.) Keefe, D. A. (Dept. Pharmacol., George Washington U., Washington, D.C.) and G. S. Edwards. *Proc Am Assoc Cancer Res* 15(March):17, 1974.

1910 REACTIONS OF ESTERS ON N-HYDROXY-2-ACETAMIDOPHENANTHRENE WITH NUCLEOSIDES AND DNA *IN VITRO*. (E.) Scribner, J. D. (Fred Hutchinson Cancer Res. Ctr., Seattle, Wash.) and N. K. Naimy. *Proc Am Assoc Cancer Res* 15(March):17, 1974.

1911 EFFECT OF CIGARETTE-SMOKING ON METABOLISM OF BENZO(a)PYRENE BY HUMAN PLACENTAL MICROSOMES. (E.) Wang, I. Y. (U. California, San Francisco), R. K. Creasy and T. T. Crocker. *Proc Am Assoc Cancer Res* 15(March):20, 1974.

1912 CORRELATION OF THE CARCINOGENICITIES OF ISOMERIC FLUORENYLHYDROXAMIC ACIDS WITH THE REACTIVITIES OF THEIR ACETATES TOWARD NUCLEOPHILES. (E.) Yost, Y. (VA Hosp., Minneapolis, Minn.) and H. R. Gutmann. *Proc Am Assoc Cancer Res* 15(March):21, 1974.

1913 TWO-DIMENSIONAL ELECTROPHORESIS OF NON-HISTONE CHROMATIC PROTEINS (NHCP) OF NORMAL, REGENERATING AND THIOACETAMIDE TREATED (TA) RAT LIVER, KIDNEY, NOVIKOFF AND WALKER 256 TUMORS. (E.) Taylor, C. W. (Baylor Coll. Med., Houston, Tex.), L. C. Yeoman, G. E. Busch, J. J. Jordan and H. Busch. *Proc Am Assoc Cancer Res* 15(March):40, 1974.

- 1914 METABOLISM OF BENZO(a)PYRENE BY MOUSE LUNG MICROSOMES. (E.) Shin, T. W. (Southern Res. Inst., Birmingham, Ala.). *Proc Am Assoc Cancer Res* 15(March):11, 1974.
- 1915 SPECIFIC METABOLISM OF BENZO(a)PYRENE DEPENDS UPON THE NATURE OF THE INDUCER OF ENZYMATIC ACTIVITY. (E.) Rasmussen, R. E. (U. California, San Francisco). *Proc Am Assoc Cancer Res* 15(March):21, 1974.
- 1916 CHEMICAL CARCINOGEN-INDUCED HYPERPLASTIC NODULES IN WHOLE MAMMARY GLAND ORGAN CULTURE. (E.) Wood, B. G. (Inst. Cell Res., U. Nebraska, Lincoln), L. L. Washburn and M. R. Banerjee. *Proc Am Assoc Cancer Res* 15(March):22, 1974.
- 1917 ONCOGENIC AGENTS FOUND IN FISH INHABITING A POLLUTED WATER SYSTEM: IMPLICATIONS FOR LEUKEMIA AND LYMPHOSARCOMA. (E.) Brown, E. R. (Chicago Med. Sch., Ill.), L. Keith, J. J. Hazdra and T. F. Sinclair. *Proc Am Assoc Cancer Res* 15(March):22, 1974.
- 1918 TUMOR INDUCTION STUDIES WITH ETHYL-, *n*-BUTYL- AND 1-CARBAMYL-2-PHENYLHYDRAZINES. (E.) Toth, B. (U. Nebraska Med. Ctr., Omaha), H. Shimizu and D. Nagel. *Proc Am Assoc Cancer Res* 15(March):23, 1974.
- 1919 INFLUENCE OF INSULIN ON GROWTH, METABOLISM AND ESTROGEN-RESPONSIVENESS IN DMBA-INDUCED MAMMARY TUMORS OF RATS. (E.) Cohen, N. D. (U. Rochester Med. Sch., N.Y.) and R. Hilf. *Proc Am Assoc Cancer Res* 15(March):23, 1974.
- 1920 ENHANCEMENT BY CAFFEINE OF *IN VITRO* TRANSFORMATION OF SYRIAN HAMSTER CELLS BY CHEMICAL CARCINOGEN. (E.) Donovan, P. J. (Nat'l. Cancer Inst., Bethesda, Md.) and J. A. DiPaolo. *Proc Am Assoc Cancer Res* 15(March):25, 1974.
- 1921 A PRODUCT OF PEROXIDATIVE TISSUE DAMAGE IS CARCINOGENIC. (E.) Shamberger, R. J. (Cleveland Clin. Fdn., Ohio), T. L. Andreone and C. E. Willis. *Proc Am Assoc Cancer Res* 15(March):26, 1974.
- 1922 TRANSPLACENTAL CARCINOGENICITY OF DMBA IN THE RAT. (E.) Joshi, S. R. (Nat'l. Cancer Inst., Bethesda, Md.), R. E. Shenefelt and J. M. Rice. *Proc Am Assoc Cancer Res* 15(March):27, 1974.
- 1923 THE METABOLISM OF THE PANCREATIC CARCINOGENS ¹⁴C-METHYL-N-NITROSOURETHANE AND METHYL NITROSUREA IN GUINEA PIGS, AND THEIR *IN VITRO* METABOLISM IN THE GUINEA PIG AND HUMAN PANCREAS. (E.) Alarif, A. (Case Western Reserve U., Cleveland, Ohio) and S. S. Epstein. *Proc Am Assoc Cancer Res* 15(March):68, 1974.
- 1924 INHIBITION OF SKIN TUMOR FORMATION WITH ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE IN INITIATION-PROMOTION CARCINOGENESIS. (E.) Curtis, G. L. (Eppley Cancer Inst., Omaha, Neb.), F. Stenback and W. L. Ryan. *Proc Am Assoc Cancer Res* 15(March):61, 1974.
- 1925 INHIBITION OF INTRACELLULAR BINDING OF PHORBOL ESTERS TO MOUSE SKIN. (E.) Slaga, T. J. (Fred Hutchison Cancer Res. Ctr., Seattle, Wash.), J. N. Rice, S. B. Das and S. Thompson. *Proc Am Assoc Cancer Res* 15(March):62, 1974.
- 1926 MUTUAL INHIBITION OF TUMOR PROMOTING ACTIVITY BY TUMOR PROMOTERS. (E.) Bock, F. B. (Roswell Park Mem. Inst., Buffalo, N.Y.) and T. C. Tso. *Proc Am Assoc Cancer Res* 15(March):64, 1974.
- 1927 AZO DYES AS POTENTIAL BLADDER CARCINOGENS. (E.) Rinde, E. (New York U. Med. Ctr., N.Y.) and W. Troll. *Proc Am Assoc Cancer Res* 15(March):65, 1974.
- 1928 ENHANCEMENT OF TUMOR GROWTH WITH DNCB IN MICE. (E.) Jessup, J. M. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.) and L. Helson. *Proc Am Assoc Cancer Res* 15(March):66, 1974.
- 1929 A CELLULAR SYSTEM FOR THE STUDY OF THE CHEMICAL REACTIVITY AND TRANSFORMING ABILITY OF BENZO(a)PYRENE AND ITS DERIVATIVES. (E.) Schechtman, L. M. (Johns Hopkins U., Baltimore, Md.), S. A. Lesko, R. J. Lorentzen and P. O. P. Ts'o. *Proc Am Assoc Cancer Res* 15(March):66, 1974.
- 1930 SKIN TUMORIGENESIS AFTER APPLICATION OF 3-METHYLCHOLANTHRENE (3MC) AND ITS K-REGION EPOXIDE; EFFECTS OF AN EPOXIDE HYDRASE INHIBITOR. (E.) Bresnick, E. (Med. Coll. Georgia, Augusta), K. Burki and G. Candelas. *Proc Am Assoc Cancer Res* 15(March):44, 1974.
- 1931 CELL CYCLE DEPENDENCE OF CHEMICALLY INDUCED MALIGNANT TRANSFORMATION *IN VITRO*. (E.) Marquardt, H. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.). *Proc Am Assoc Cancer Res* 15(March):45, 1974.
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See also:

- * (Rev): 1803, 1806, 1809, 1813, 1816, 1820
- * (Viral): 2034
- * (Immun): 2138, 2159, 2165, 2167, 2180, 2245
- * (Epid-Biom): 2269, 2271, 2284, 2286, 2287

2000 CAUSE OF DEATH IN RADIOLOGICAL WORKERS;
ANALYSIS OF CAUSE OF DEATH IN JAPANESE
RADIOLOGICAL TECHNICIANS, 1966 TO 1972. (E.)
Kanabatake, T. (Niigata U. Sch. Med., Japan) and
T. Watanabe. *Acta Med Biol (Niigata)* 21(2):107-111,
1973.

Data from the Japan Radiological Technicians Association were analyzed to determine the death rates from radiation injury of radiology technicians during the yrs 1966-72. During this time period, 134 deaths were reported, a value considerably less than expected, presumably due to inadequate reporting. Of these deaths, 6 were due to skin cancer and 2 to aplastic anemia, rates higher than expected based on death rates in the normal population. Five cases of leukemia were reported, a value which did not significantly differ from expected. The average age of death among radiology technicians between 1966-72 was 52.7 yr compared with the expected 48.6 yr, an insignificant difference.

2001 THE EFFECT OF INTERNALLY DEPOSITED PLUTONIUM-239 ON THE LYSOSOMES OF RAT LIVER. (E.) Danpure, C. J. (Inst. Cancer Res., Sutton, Surrey, England) and D. M. Taylor. *Radiat Res* 59 (3):679-692, 1974.

The effects of plutonium-239, an α -particle emitting radionuclide which deposits mainly in the lysosomes, on the activity of various lysosomal enzymes have been studied in rat liver. The effects observed have been compared with those produced by the β + γ radiation from colloidal gold-198. Following i.v. administration of 0.5 μ C polymeric ^{239}Pu , the specific activities of acid deoxyribonuclease and aryl sulphatase of liver homogenates from sacrificed rats were increased by 30 days and remained elevated at 1 yr. β -Glucuronidase, acid β -glycerophosphatase, and cathepsin D showed increased specific activity at time intervals longer than 6 mo after injection of ^{239}Pu . All the enzymes studied showed decreased sedimentation rate in 0.25 M sucrose at 30 days but this returned to approximately normal limits at longer time intervals. In comparison the administration of 0.5 mC ^{198}Au colloid also caused increased specific activity of deoxyribonuclease II, β -glucuronidase, and acid β -glycerophosphatase, but did not decrease the enzyme sedimentabilities. It is concluded that at least some of the pathological effects known to be produced by ^{239}Pu and ^{198}Au may be explained in terms of lysosomal changes.

2002 THE SKELETAL DOSE FROM ^{224}Ra FOLLOWING INTRAVASCULAR ADMINISTRATION OF THOROTRAST. (E.) Rowland, R. E. (Radiol. Environ. Res. Division, Argonne Natl. Lab., Ill.) and J. Rundo. *Proc Third Int Meeting Toxicity Thorotrast, Copenhagen, Denmark* pp. 95-103, April, 1973.

With the use of a set of "best estimates" of the distribution of ^{232}Th and its daughters in the marrow-free skeleton following i.v. administration of Thorotrast, the dose to bone from "translocatable" ^{224}Ra has been calculated. "Translocatable" ^{224}Ra is that

radium created *in vivo* that is free to translocate, that is, equivalent to systemically injected Ra. The accumulated dose to bone from this ^{224}Ra 25 yr after injection of 25 ml of Thorotrast is of the order of 25 rads. A linear dose-effect relationship for the appearance of bone tumors in man has been postulated from the observed tumor incidence in the series of patients injected with ^{224}Ra in Germany. This linear hypothesis predicts more bone tumors in Thorotrast cases than are observed, implying either that the relationship is not linear at low doses or that at very low dose rates the effect per rad is lower than predicted.

2003 OSTEOGENIC SARCOMA DEVELOPING AFTER RADIOTHERAPY FOR RETINOBLASTOMA. (E.) Shah, I. C. (Mem. Hosp. Sloan-Kettering Cancer Ctr., New York, N.Y.), M. Arlen and T. Miller. *Am Surg* 40(8):485-490, 1974.

Two cases of osteogenic sarcoma following radiotherapy for retinoblastoma are reported. In the first case, the tumor occurred after a latent period of 23 yr following radiotherapy. The patient died 14 months after the appearance of the osteogenic sarcoma. In the second case, the tumor occurred after a latent period of seven yr. The second patient lived for 32 months following surgical therapy for sarcoma. This entity is extremely rare; 11 cases have been reported in the literature.

2004 THE DISTRIBUTION IN THE CELL CYCLE OF NORMAL CELLS AND OF IRRADIATED TUMOUR CELLS IN MICE. (E.) Raju, M. R. (Los Alamos Sci. Lab., U. California, N.M.), T. T. Trujillo, P. F. Mullaney, A. Romero, A. Steinkamp and R. A. Walters. *Br J Radiol* 47(559):405-410, 1974.

Flow microfluorometry (FMF) instrumentation was used to make a rapid, quantitative measurement of the DNA content of individual cells from normal tissues and mouse KHT tumor cells. The normal tissues studied are some of the limiting normal tissues in radiation therapy. The DNA content of the tumor cells was also measured at different times after X-ray exposure. Preliminary results indicated that the cellular DNA content of all normal tissues was about the same and that a large fraction of cells were in the G_0 or G_1 stage. In the KHT cells, nearly 75% of the cells were in the G_0 or G_1 stage, 20% were in the S stage, and the remaining 5% were in the G_2 + M stage. Ten hours after exposure to 300 rads, the number of tumor cells in the G_1 stage decreased to about 40%, the number of cells in the G_2 + M stage increased to about 30%, and the number of cells in the S stage increased to about 30%. The cellular DNA content was very nearly the same as in nonirradiated controls 24 hours after exposure. When the tumors were exposed to 3,500 rads, the number of cells in the S stage 24 hours after exposure was 25%, while the number of cells in the G_2 + M stage increased to about 50%. FMF instrumentation can be a useful tool in obtaining quantitative information regarding DNA distribution and normal and tumor cell kinetics during radiation treatment.

2005 MALIGNANT AND BENIGN NEOPLASMS OF THE THYROID IN PATIENTS TREATED FOR HYPERTHYROIDISM: A REPORT OF THE COOPERATIVE THYROTOXICOSIS THERAPY FOLLOW-UP STUDY. (E.) Dobyns, B. M. (Cleveland Metropolitan Gen. Hosp., Ohio), G. E. Sheline, J. B. Workman, E. A. Tompkins, W. M. McConahey and D. V. Becker. *J Clin Endocrinol Metab* 38(6):976-998, 1974.

Data concerning the occurrence of malignant and benign thyroid neoplasms in patients treated for hyperthyroidism have been collected at 26 medical centers in the Cooperative Thyrotoxicosis Therapy Follow-Up Study. There was 98.8% follow-up in 36,050 patients treated for hyperthyroidism between 1946 and 1968 by ^{131}I , thyroidectomy, antithyroid drugs, X-irradiation or various combinations of these measures. There were 86 malignant thyroid neoplasms found among the 34,684 patients. There were 9 malignant thyroid neoplasms found within 1 yr of treatment in 21,714 patients treated by ^{131}I , 50 in 11,732 patients treated by thyroidectomy, and none in 1,238 patients treated with antithyroid drugs. After an interval of more than 1 yr there were 19 malignant thyroid neoplasms following ^{131}I , 4 following thyroidectomy and 4 following antithyroid therapy in these respective populations. If the occurrence of 19 malignant lesions found 1 yr or more after ^{131}I is viewed from the standpoint of the incidental malignant lesions found in patients treated primarily by thyroidectomy, the risk from ^{131}I is not significant.

2006 NORMAL AND X-IRRADIATED TRACHEAL GRAFTS AND THEIR USES. (E.) Nair, B. K. (Coll. Med., U. California, Irvine) and T. T. Crocker. *J Natl Cancer Inst* 53(3):887-891, 1974.

Mouse tracheas were grafted in mouse mammary fat pads and hamster tracheas were grafted in hamster cheek pouches. In both instances, the grafts were maintained in a healthy condition for more than 1 yr. When the hamster tracheas were irradiated (600 rads/min) and grafted, the normal, pseudostratified, ciliated, columnar epithelium atrophied, leaving only a thin layer of flat cells that maintained the basement membrane. The lethal effect of x-rays was dose dependent. At 2000 or 4000 rads, 50-60% of the epithelium lost the pseudostratified, columnar, ciliated condition within 2 wk. At 6000 and 8000 rads pronounced changes appeared in the epithelium, the nuclei of the basal cells became elongated and in some instances pleomorphic. DNA synthesis was inhibited but not eliminated by x-rays. The cytoplasm was vacuolized and swollen, the nuclei were pyknotic, and giant cells formed. The "epithelium-free" irradiated grafts are being used as a matrix for epithelial-mesenchymal interaction studies and nonirradiated grafts are being used for experiments on tracheobronchial carcinogenesis.

2007 AEROSOLS IN SKY POSE DOWN-TO-EARTH THREAT. (E.) Anonymous. *Chem Week* 115(12):59, 1974.

In a report before this year's meeting of the Ameri-

can Chemical Society, F.S. Rowland warned of the potential hazard of widespread use of aerosol spray cans. The problem stems from the fact that they contain chlorofluoromethanes as propellants. These substances drift into the upper atmosphere where decomposition by UV light causes release of chlorine atoms that destroy the ozone layer which filters harmful UV rays originating from the sun. It was estimated that a 5% reduction of the ozone layer could result in 8000 extra U.S. skin cancer cases/yr. If chlorofluoromethane production continues at the present rate, the ozone layer could drop by 10% by the yr 2000. The reduced ozone might also cause a change in the atmosphere's heat balance which could lead to unpredictable changes in the world weather patterns.

2008 ANOTHER DISASTER THREATENS. (E.) Plant, A. F. (No affiliation). *Chem Eng News* 52(39):2, 1974.

By 1990, the depletion of the ozone layer in Earth's upper stratosphere could reach 5%. The dominant factor in this depletion will theoretically be the chlorine derived from sunlight-induced chlorofluorocarbon aerosol propellant breakdown. Halting the dispersal of these propellants would be practically and commercially feasible by the end of this decade at the earliest. A 10% reduction in the ozone layer would result in an increase of 8000 skin cancer cases per year among the white population of the United States. Thus, there is an urgent need for further investigations into the problem. If the theoretical assessments appear valid on the basis of such investigations, propellant use must be eliminated as quickly as possible. At the same time, methods of moderating or eliminating the chlorofluorocarbon reactions which are causing the problem should be investigated.

2009 ESR SIGNALS DURING X-IRRADIATION OF TISSUE: THEIR CHARACTERISTICS AND RELATIONSHIP TO THE CANCEROUS STATE. (E.) Floyd, R. A. (Ctr. Biol. Natural Systems, Washington U., St. Louis, Mo.), A. Bronsdon and B. Commoner. *Ann NY Acad Sci* 222:1077-1086, 1974.

Previous studies have revealed certain striking differences in the character and kinetic behavior of the free radicals generated by the x-irradiation of radiosensitive tissues as compared with less sensitive ones. Immediately on x-irradiation, sensitive rat testis homogenates exhibited a free radical signal (the doublet of the free radical, semidehydroascorbate) which decayed to about 60% of the original value after 10 minutes of x-irradiation and decayed immediately when the irradiation ceased. When ascorbate (20 mM) was added to the testis preparation, a small doublet was present before and after irradiation; this became very prominent during x-irradiation and did not decline during irradiation. Adding ferricyanide to the tissue homogenate prevented the appearance of the doublet during irradiation, while the intensity of the irradiation-induced signal was reduced in proportion to the amount of flavin mono-

nucleotide added to the preparation. The signal did not appear when the tissue was frozen, but it was about equally strong at 0 and 15 C. 5-(2-aminoethyl)-isothiuronium (10 mM) increased the intensity of the signal by 25%, while cysteamine increased the signal by 17% at a concentration of 10 mM, but abolished it at a concentration of 250 mM. The amplitude of the doublet decreased with time at irradiation intensities of 3.9, 2.5, and 1.9 krad/sec; at 1.1 krad/sec, the amplitude of the signal increased slightly with time. While normal liver tissue exhibited no ascorbate free radical on irradiation, liver tumor tissue did. The data indicate that the radiosensitivity of testis tissue is related to the function of the ascorbate free radical, which is in turn influenced by the tissue flavin content. The effect of x-irradiation on liver tumor tissue probably reflects a difference in the redox environment of ascorbate in normal and tumor tissue during irradiation.

2010 ANALYSIS OF CELL KINETICS DURING ULTRAVIOLET LIGHT-INDUCED EPIDERMAL CARCINOGENESIS IN HAIRLESS MICE. (E.) Chopra, D. P. (Temple U. Hlth. Sci. Ctr., Phila., Pa.) and P. D. Forbes. *Cancer Res* 34(3):454-457, 1974.

Proliferation kinetics at various stages of UV light-induced squamous cell carcinoma in hairless mice were studied by a double-labeling method. In irradiated mice, the growth fraction, as determined by continuous labeling with thymidine-³H, was 100% in normal-appearing and hyperplastic epidermis and in lesions of squamous cell carcinoma. The growth fraction in control unirradiated mice was also 100%. The duration of the cell generation time (T_c) and the DNA synthetic phase (S) decreased progressively with induction and progression of the tumor. For normal-appearing epidermis of irradiated mice and epidermis of control mice, T_c and S were approximately 95 and 6.2 hr, respectively. With the induction of hyperplasia, T_c and S were reduced to 43.75 and 4.45 hr, respectively, while even lower values were obtained for squamous cell carcinoma where T_c = 16 hr and S = 3.05 hr. The labeling index in normal epidermis was 6.75% and increased progressively in hyperplastic epidermis (10.17%) and squamous cell carcinoma (18.98%). These results indicated that ultraviolet light-induced epidermal tumor production in hairless mice is associated with a progressive shortening of the cell cycle.

2011 THE EFFECTS OF IMMUNOSUPPRESSION BY ANTI-THYMOCYTE SERUM (ATS) ON SPONTANEOUS AND RADIATION-INDUCED NEOPLASTIC DISEASES IN MICE. (E.) La Plant, P. R. (Lawrence Berkeley Lab., U. California) and L. S. Kelly. *Proc Am Assoc Cancer Res* 15(March):119, 1974.

2012 CHRONIC MYELOGENOUS LEUKEMIA (CML) DEVELOPING AFTER THYMIC IRRADIATION. (E.) Shimaoka, K. (Roswell Park Mem. Inst., Buffalo, N.Y.) and J. E. Sokal. *Proc Am Assoc Cancer Res* 15(March):131, 1974.

See also:

- * (Rev): 1804, 1818, 1823
- * (Chem): 1940, 1966
- * (Epid-Biom): 2274

- 2013 PULMONARY CARCINOMA (JAAGSIEKTE) OF SHEEP: PATHOLOGIC FINDINGS AND COMPARISON IN MULTIPLE-CASE AND CASE-FREE HERDS. (E.) Hod, I. (Hebrew U. Jerusalem, Rehovot, Israel), A. Zimber, U. Klopfer, A. W. Helder, T. A. Nobel and K. Perk. *J Natl Cancer Inst* 53(1):103-110, 1974.

During a 2-yr intensive study of three herds of sheep, alveolar cell carcinoma (lung carcinoma, pulmonary adenomatosis, jaagsiekte) occurred in only one herd. This herd also had the highest incidence of various other diseases, such as verminous pneumonia, lung abscesses, chronic interstitial pneumonia, and mediastinal lymphadenitis due to *Cornibacterium-ovis*. Hyper-7S immunoglobulinemia as defined by ultracentrifugal and immunoelectrophoretic analyses was used to indicate diseased animals. In the highly diseased herd, 46 of 550 animals were "hyperimmune." Postmortem examination of 16 diseased animals revealed nine jaagsiekte cases and seven other diseases. The other two herds each with 350 animals were "case free." Virus-like particles, similar to the murine C-type virions, were observed in the primary tumor tissue.

- 2014 *IN VIVO* GROWTH AND ANTIGENIC PROPERTIES OF A RAT SARCOMA INDUCED BY MOLONEY SARCOMA VIRUS. (E.) Jones, J. M. (Scripps Clin. Fdn., La Jolla, Calif.), F. Jensen, B. Veit and J. D. Feldman. *J Natl Cancer Inst* 52(6):1771-1777, 1974.

The growth and antigenic properties of a BN Moloney sarcoma (MST) were examined in syngeneic (BN) and allogeneic (Lewis) rats. In BN rats, MST doses of 5×10^6 cells and higher were invariably fatal, and tumor growth was most rapid when MST was injected i.p. Lewis rats were completely resistant to MST doses up to 5×10^7 cells. Lewis rats produced a greater cell-mediated cytotoxicity response than did BN rats, directed chiefly to AgB antigens, and they yielded less anti-gs-1 antibody. Growth of MTS in BN rats was inhibited by immune spleen cells and MP lectin, was not affected by phytohemagglutinin or concanavalin A, and was enhanced by immune serum. Lewis rats, hyperimmunized with MST, produced antibody to alloantigens and to tumor-specific and virus-related antigens. Antitumor antibody could be eluted from growing solid tumors of either host. Studies with enriched radiolabeled anti-AgB antibody showed that MST cells carried about 50% of the allo-antigen content of normal BN cells, but that amount was sufficient to provoke a brisk immune response in Lewis rats.

- 2015 REPLICATION OF MAREK'S DISEASE VIRUS IN CELL CULTURES DERIVED FROM GENETICALLY RESISTANT CHICKENS. (E.) Sharma, J. M. (Regional Poultry Res. Lab., Agr. Res. Serv., East Lansing, Mich.) and H. G. Purchase. *Infect Immun* 9(6):1092-1097, 1974.

Various parameters of replication were compared on a chronological basis in cell-free and cell-associated

preparations of three strains of pathogenic Marek's disease virus (MDV) (JM, GA, ID-1) in cell cultures of genetically resistant (line 6) and genetically susceptible (line 7) chickens, and the pathogenicity of MDV propagated in cells of resistant chickens was tested. Cell-free and cell-associated preparations of the three strains of MDV replicated equally well in the cells of resistant and susceptible chickens. There were no demonstrable differences between the two types of cells in terms of the chronological appearance and type of cytopathic effects or the type of virus-induced antigens detectable by immunofluorescence and agar-gel precipitin tests. MDV propagated for about 4 wk in the cells of the line 6 chickens, remaining nonvirulent for the resistant chickens and fully virulent for the susceptible chickens. The lack of expression of genetic resistance to Marek's disease at the cellular level contrasts the infection mechanisms of MDV with those of viruses associated with lymphoid leukosis in chickens. Genetic resistance to MD may occur because: the target cell is lacking in the resistant host; the target cell exists but fails to undergo modifications necessary for tumor induction; or the virus modifies the target cell and initiates a response, but the resistant host has effective means of preventing the lesions.

- 2016 OF BIRDS AND MICE AND MEN: COMMENTS ON THE USE OF ANIMAL MODELS AND MOLECULAR HYBRIDIZATION IN THE SEARCH FOR HUMAN TUMOR VIRUSES. (E.) Bishop, J. M. (Dept. Microbiol., U. California, San Francisco), N. Quintrell, E. Medeiros and H. E. Varmus. *Cancer* 34(4):1421-1426, 1974.

Two paradigms of viral oncogenesis hold that: it is accomplished by the introduction of genetic information into the cell; and that genes homologous to those present in the genomes of laboratory strains of RNA tumor viruses reside in the chromosomes of all normal cells, some of these genes becoming oncogenic when activated. The first is supported by the fact that the infection of either duck or mammalian cells with Rous sarcoma virus (RSV) introduces a new set of genes into the chromosomal DNA of the host cell; this event is a prerequisite for both replication of the virus and neoplastic transformation of the cells. The second paradigm is supported by the fact that virus-induced mammary carcinoma in the mouse can be an inherited disease requiring no genetic information beyond that already present in the mouse genome. Both paradigms are based on the view that RNA tumor virus genes are perpetuated in the host cell as a DNA provirus. Molecular hybridization experiments have shown that, with few exceptions, RNA tumor viruses from different species do not share physically detectable genetic homology. However, the discovery of appreciable homology between the genome of the murine leukemia virus (MuLV) and certain primate C-type viruses indicates that cross-species hybridization may yet prove useful. Although a small amount of hybridization between the murine mammary tumor virus (MMTV) DNA and RNA extracted from human breast carcinomas has been found using relatively nonstringent assay conditions, the nucleotide sequences in the genome of MMTV are too specific to warrant extensive use of

murine reagents in the analysis of human breast carcinoma. Molecular studies should be conducted in tandem with biological and genetic analysis of both known and yet-to-be-discovered cancer viruses.

- 2017 EFFECTS OF INDOMETHACIN ON MOLONEY SARCOMA VIRUS-INDUCED TUMORS. (E.) Humes, J. L. (Dept. Zool. Physiol., Rutgers U., Newark, N.J.), J. J. Cupo, Jr. and H. R. Strausser. *Prostaglandins* 6(6):463-473, 1974.

Male BALB/cJ mice were injected i.m. in the right hind leg with a Moloney sarcoma virus (MSV) preparation. Beginning the next day, they were injected every other day s.c. with about 5 mg/kg of the prostaglandin (PG) inhibitor indomethacin. Indomethacin significantly delayed the onset of tumor development and significantly inhibited tumor growth. In animals inoculated with MSV alone, the PG content of the MSV-induced sarcoma paralleled the growth of the tumor, as did the cyclic AMP levels. Indomethacin severely inhibited (91%) the elevation of the PGF levels in the MSV-induced sarcomas, and depressed the corresponding PGE levels by 67%. There was no change in the levels of the cyclic nucleotides. Administration of antilymphocyte serum (ALS) to the mice at the time of MSV inoculated resulted in accelerated and enhanced tumor growth. Indomethacin treatment in these animals suppressed tumor growth, but less dramatically than in animals which had not been treated with ALS. These results indicate that the immune system is necessary for tumor regression, that PG acts to promote tumor growth, and that the synergistic action of the immune system and indomethacin treatment suppresses tumor growth.

- 2018 MUTANTS OF NONPRODUCER CELL LINES TRANSFORMED BY MURINE SARCOMA VIRUS. III. DETECTION AND CHARACTERIZATION OF RNA SPECIFIC FOR HELPER AND SARCOMA VIRUSES. (E.) Tsuchida, N. (Flow Labs., Inc., Rockville, Md.), M. Shih, R. V. Gilden and M. Hatanaka. *J Exp Med* 140(1):218-224, 1974.

BALB/3T3 cells transformed by the Kirsten sarcoma virus (Ki-SV) (non-virus producer BALB/3T3 cells) and mutant cell lines derived therefrom following treatment with 5'-bromodeoxyuridine (BrdU) were analyzed for the expression of virus-specific RNA using single-stranded DNA transcripts of Rauscher leukemia virus (RLV), a virus activated in one of the cell lines (58-2T), and Ki-SV-specific DNA transcript (after removal of all sequences cross-reactive with RLV DNA). The Rauscher virus DNA detected multiple copies of viral RNA in virus-producing cells (about 2.5×10^3 /cell) whether infected with RLV or activated to produce virus with BrdU. Nonproducer (NP) cells and normal BALB cells showed small numbers of RNA genomes (70-250/cell) and only partial saturation of the transcript. The intracellular RNA sedimented at 35S (main peak) with a variable minor peak at 20S with the exception of one mutant cell, M-43-2, which showed a main peak at 26-27S. The 58-2T transcript reacted preferentially in NP cells and their derivatives with bi-

phasic kinetics suggesting the possibility of sequences specific for the original transforming virus. The size of the Ki-SV specific sequences was 30S in the mutant cells whether or not complete virus was being produced and independently of *in vivo* transplantability.

- 2019 EVIDENCE FOR A REGULATORY FUNCTION RELATED TO THE EXPRESSION OF THE POLYOMA GENOME FOLLOWING THE ONSET OF VIRUS DNA REPLICATION. (E.) Rutherford, R. B. (U. Rochester Sch. Med. Dentistry, N.Y.). *Biochem Biophys Res Commun* 58(3):839-846, 1974.

DNA-RNA hybridization was used to measure the amounts of virus specific RNA synthesized in permissive cells (secondary mouse embryo fibroblasts) at various times after infection by the 3049 strain of polyoma virus. The virus-specific RNA was measured using the "ternary complex" assay technique. When compared with cells infected with a control, wild-type virus, cells infected with the 3049 virus contained virus-specific polyadenylated nuclear and polysomal RNA following the onset of DNA synthesis. Prior to the onset of DNA synthesis, no difference in the quantity of virus-specific, polyadenylated RNA was observed. These findings support the hypothesis that the 3049 strain of polyoma virus represents a unique variant in which the phenotype reflects an alteration in the regulation of expression of the polyoma genome following the onset of viral DNA synthesis.

- 2020 ADULT AND EMBRYONIC GECKO CELLS *IN VITRO*: GROWTH CHARACTERISTICS, INFECTION BY RABIES, SINDBIS AND POLYOMA VIRUSES, AND TRANSFORMATION BY SV40. (E.) Michalski, F. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), M. M. Cohen and H. F. Clark. *Proc Soc Exp Biol Med* 146(2):337-348, 1974.

Cell lines were established from trypsin-dispersed or minced and explanted tissues of whole embryo or adult tail tissues of the leopard gecko, *Eublepharis macularis*. Embryo cells grew more rapidly at early passage levels, but an adult cell line exhibited a growth rate similar to that of embryonic cells after adaptation to *in vitro* growth for 12 passages. The embryo cells were predominantly epithelial-like, while the cells of adult origin were fibroblast-like. The two cell lines could not be distinguished on the basis of temperature optimum, medium pH requirements, karyotypic changes, or virus susceptibility. The adult and embryonic cells supported cytopathic infection by vaccinia, herpes simplex, frog polyhedral, Newcastle disease, Sindbis, and vesicular viruses. Single step growth curves of Sindbis virus were identical in adult and embryonic *Eublepharis* cells incubated at 33 C, but were different from curves obtained from other reptilian and mammalian cells. Both the adult and embryonic cells supported abortive rabies virus infection. SV40 caused transformation at a similar rate in adult and embryonic cells incubated at 30 C. The transformed cells exhibited 100% T antigen expression, morphologic and

karyotypic alterations, increased cell saturation density, absolute plating efficiency, and efficiency of colony formation in soft agarose. Tumor-specific transplantation antigen induction was not evident. The adult fibroblasts transformed *in vitro* by SV40 did not cause tumors when reinoculated into the allogeneic host animal. Gecko cell cultures infected with polyoma virus at 30 C exhibited $\leq 1\%$ T antigen expression which persisted for 25 cell passages, but did not lead to transformation.

- 2021 TRANSLATION OF mRNA FROM SIMIAN VIRUS 40-INFECTED CELLS INTO SIMIAN VIRUS 40 CAPSID PROTEIN BY CELL-FREE EXTRACTS. (E.) Lodish, H. F. (Dept. Biol., Massachusetts Inst. Technol., Cambridge), R. Weinberg and H. L. Ozer. *J Virol* 13(3):590-595, 1974.

Messenger RNA was isolated from simian virus 40 (SV 40)-infected and mock-infected Vero cells by chromatography on poly(U) sepharose. When added to cell-free extracts from Chinese hamster ovary cells or rabbit reticulocytes, RNA from the infected cells, but not from the mock-infected cells, stimulated synthesis of the major SV40 capsid protein. Identification of this species was achieved by sodium dodecyl sulfate gel electrophoresis, peptide mapping, and immunoprecipitation. The *in vitro* synthesized capsid protein was slightly different from virion assembled capsid protein, as shown by separation following chromatography on hydroxylapatite and by minor differences in the peptide map. It is possible that during *in vivo* virus assembly, the capsid protein may be modified by loss of some amino acids and thus generate a soluble methionine-containing tryptic peptide from the insoluble tryptic core of the precursor protein. It is also possible that the virus capsid is methylated at some stage during assembly, resulting in the appearance of the new (^3H)methionine-labeled peptide found during hydroxylapatite chromatography.

- 2022 ISOLATING OF DEFECTIVE VIRUSES FROM SV40-TRANSFORMED HUMAN AND HAMSTER CELLS. (E.) Huebner, K. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), C. M. Croce and H. Koprowski. *Virology* 59(2): 570-573, 1974.

Simian virus 40 (SV40)-transformed human and hamster nonyielding cell lines were fused with green monkey kidney cells and the heterokaryocytes seeded in green monkey kidney cell monolayers for the detection of plaques due to infectious centers. Three weeks after incubation, very small (micro) plaques were seen which microscopically resembled SV40 plaques. Virus from these microplaques was transferred and grown in TC7 cells. Neither SV40 tumor nor capsid antigens were detectable by indirect fluorescent antibody staining 1-6 days after infection. These data indicate that if the entire SV40 genome is present in the SV40-transformed cells from which the microplaque virus could be isolated, it must be in a form which can never be completely or properly excised.

- 2023 SENSITIVITY TO GUINEA-PIG SERUM OF HAMSTER CELLS TRANSFORMED *IN VITRO* BY TWO STRAINS OF THE ROUS SARCOMA VIRUS. (E.) Bataillon, G. (Inst. Radium, Fac. Sci., Orsay, France). *Int J Cancer* 13(1):9-15, 1974.

The sensitivity of untransformed BHK 21/13 cells to the cytotoxic action of normal guinea-pig (GP) serum was compared with that of BHK 21/13 cells transformed *in vitro* by the Bryan (RB 12) and Schmidt-Ruppin (RS 2) strains of Rous sarcoma virus (RSV). Whereas the cloning efficiency of the BHK 21/13 cells in soft agarose was greatly reduced when the cells were preincubated with GP serum, the RS 2 cells were much less affected and the RB 12 cells were unaffected by the same treatment. Mild treatment of the cells with *Vibrio cholerae* neurominidase, which did not affect the sensitivity of the BHK 21/13 and RS 2 cells, rendered the RB 12 cells significantly sensitive to the cytotoxic action of the normal GP serum. The GP serum appears to contain heterospecific cytotoxic substances which are directed against a xenogeneic surface antigen present on the BHK 21/13 cells, and to a lesser extent, on BHK 21/13 cells transformed by the SR-RSV. This antigen is not detectable on the surface of BHK 21/13 cells transformed by the B-RSV, but it can be "unmasked" after treatment with neuraminidase.

- 2024 RETICULUM CELL SARCOMAS INDUCED IN MICE BY RAUSCHER VIRUS. (E.) Dawson, P. J. (Stanford Res. Inst., Menlo Park, Calif.) and A. H. Fieldsteel. *J Natl Cancer Inst* 52(6):1805-1809, 1974.

Transplantable reticulum cell sarcomas were established from mice with advanced Rauscher disease by s.c. implantation of spleen fragments into syngeneic recipients. Six tumors developed among 96 (C57BL/6 x DBA/2) F_1 (B6D2 F_1) and (C57BL/Ks x DBA/2) F_1 (BkD2 F_1) recipients. Three transplantable lines were established morphologically and biologically resembling similarly produced tumors from spleens of B6D2 F_1 mice with advanced Friend disease. Light and electron microscopy of the transplantable cell lines showed primitive hematopoietic or lymphoreticular cells, and all three lines contained Rauscher virus. These tumors were different from the transplantable myeloid and lymphatic leukemias reported previously in mice inoculated with Rauscher virus. Attempts to establish reticulum cell sarcomas by the same technique in 119 BALB/c mice were uniformly unsuccessful.

- 2025 EVIDENCE FOR VIRUS-SPECIFIC TRANSPLANTATION ANTIGEN IN CELLS OF LYMPHOID NEOPLASMS INDUCED BY PAPOVAVIRUS SV40. (E.) Tevethia, S. S. (Tufts U. Sch. Med., Boston, Mass.). *Int J Cancer* 13(4):494-499, 1974.

Syrian hamster lymphocyte leukemia and lymphosarcoma cells induced *in vivo* by the i.v. inoculation of live papovavirus SV40 (simian virus 40) were tested for the presence of SV40-specific transplantation antigen. The cells derived from the lymphocytic leukemia (GD-

248) blocked primary SV40 oncogenesis *in vivo* in adult Syrian hamsters and also immunized adult hamsters against the transplantation of SV40 tumor cells which have been shown to carry SV40-specific transplantation antigen. The lymphosarcoma cells (GD-36), although immuno-sensitive, were not effective in blocking SV40 oncogenesis. The GD-36 cells were also less immunogenic than the GD-248 cells. These results indicate that the appearance of lymphoid cell tumors in adult hamsters by SV40 is not due to the absence of SV40-specific transplantation antigen in these tumors. A more probable explanation for the development of tumors in adult animals by SV40 may be the presence of blocking factors synthesized early during tumorigenesis and by the possibility that the administration of the virus i.v. may favor the formation of such factors.

2026 ROUS SARCOMA VIRUS-TRANSFORMED HAMSTER TUMOR CELLS RESISTANT TO 5-BROMO-DEOXYURIDINE. (E.) Kuwata, T. (Sch. Med., Chiba U., Japan), N. Morinaga, T. Okazaki and R. Ishitani. *J Natl Cancer Inst* 52(6):1763-1770, 1974.

Rous sarcoma virus (RSV)-transformed hamster sarcoma cells, H-BK strain, were cultured, and induction of RSV by 5-bromodeoxyuridine (BUDR) treatment was attempted. After continuous treatment of the H-BK cells, BUDR-resistant lines were isolated, and biologic characteristics of three resistant lines were studied. BUDR-resistant cells, maintained with 50 μ g/ml BUDR, did not produce infectious RSV. However, they harbored RSV genomes. When these cells were inoculated into wing webs of chicks, their tumorigenicity was almost the same as that of the BUDR-sensitive parent cells. Moreover, the three resistant lines showed the same degree of transplantability to hamsters and agglutinability by concanavalin A as the parent strain.

2027 A DETERMINATION OF THE OUTER DIMENSIONS OF ONCORNAVIRUSES BY SEVERAL ELECTRON MICROSCOPIC PROCEDURES. (E.) Luftig, R. B. (Worcester Fdn. Exp. Biol., Shrewsbury, Mass.), P. N. McMillan, K. Culbreth and D. P. Bolognesi. *Cancer Res* 34(7):1694-1706, 1974.

The effect of negative stain, freeze-fracture, and thin-sectioning procedures on the size of several oncornaviruses was determined. The estimated size ranges for three classes of oncornaviruses are: (a) 1250 to 1450 Å, for avian C-type viruses (avian myeloblastosis virus (AMV) and Rous sarcoma virus, Prague strain); (b) 1350-1550 Å, for murine C-type viruses (Friend leukemia virus (FLV) and Moloney leukemia virus); and (c) 1200-1400 Å, for B-type viruses (mouse mammary tumor virus). Concomitant studies of oncornavirus cores indicated a clear difference between avian and murine type viruses. AMV cores measured about 730 Å in diameter and had a ribonucleoprotein component that was centrally collapsed. FLV cores in contrast measured about 840 Å and appeared to have the ribonucleoprotein closely associated with the core shell. These results suggest

that the 100-Å smaller value obtained for the outer dimension of avian viruses is due to the presence of a smaller core component.

2028 CHARACTERISTICS OF THE INTRACELLULAR STRUCTURES IN CELLS OF HUMAN ORIGIN, PRODUCING ONCORNAVIRUS TYPE B. (E.) Bukrinskaya, A. G. (Acad. Med. Sci. USSR, Moscow), G. G. Miller, E. N. Lebedeva and V. M. Zhdanov. *Dokl Akad Nauk SSSR, Biol Sci* 213(1/6):574-576, 1973.

The results of a study of the intracellular structures isolated from a transplantable line of cells of human origin, Detroit-6, are presented. The method that was used for extraction of RNA from intracellular structures after equilibrium centrifugation permitted the isolation of virus-specific RNAs, 35S and 60S, free of impurities of cellular ribosomal RNAs. The structures that were detected, with buoyant density 1.23, 1.21 and 1.19 g/ml, possess reverse transcriptase activity in the absence of detergent and did not contain proteins blocking the polymerase activity. These structures seem to be the precursors of the mature virions. Structures with a density of 1.23 g/ml were identified as type A nucleoids. The 60S RNA contained in the structures may be a substantially better matrix for reverse transcriptase than the 35S RNA. The absence of 70S RNA in the intracellular particles confirms previous data on the extracellular "maturation" of RNA within the budded-off virion.

2029 THE CONSEQUENCES OF ALTERED GALACTOSE METABOLISM IN ONCORNAVIRUS-TRANSFORMED CELLS. (E.) Blair, C. D. (Baylor Coll. Med., Houston, Tex.), P. J. Brennan, S. Steiner and M. Benyesh-Melnick. *Biochem Soc Trans* 2:731-732, 1974.

Normal rat embryo cells and murine sarcoma-leukemia virus-transformed cells were grown for at least 12 hr in medium containing 14 C-galactose, then separated into a low-molecular wt soluble fraction, glycolipid, and an insoluble glycoprotein-polysaccharide fraction. The glycolipids of both normal and transformed cells had similar ratios of 14 C-glucose to 14 C-galactose. However, while the insoluble fraction of the normal cells had a 2:1 ratio of 14 C-glucose to 14 C-galactose, the ratio in the transformed cells was about 1:3. In the normal cells, nonglycolipid 14 C-glucose was associated only with the cytoplasmic fraction; in transformed cells, this was almost completely replaced by 14 C-galactose. Compared with normal chick embryo fibroblasts, Rous sarcoma virus-transformed chick embryo cells had the same altered glucose to galactose relationship in the glycoprotein-polysaccharide fraction. Cells infected by a transformation-defective variant of Rous Sarcoma virus produced virus but did not display the altered morphology and growth rate typical of transformation or any deviation from the normal cell pattern. Galactose became predominant 42-54 hr after infection with Rous sarcoma virus, the same period when transformation became visually apparent. Residual carbohydrate segments of cytoplasmic glyco-

protein-polysaccharide fractions from rat cells were examined by gel filtration. The component which eluted last, which may be akin to the glucosyl-galactosyl disaccharide chains of collagen, shifted to a slightly lower molecular wt position in transformed cells.

- 2030 EVIDENCE FOR GENETIC RECOMBINATION BETWEEN ENDOGENOUS AND EXOGENOUS MOUSE RNA TYPE C VIRUSES. (E.) Stephenson, J. R. (Nat'l. Cancer Inst., Bethesda, Md.), G. R. Anderson, S. R. Tronick and S. A. Aaronson. *Cell* 2(2):87-94, 1974.

Two viruses isolated following prolonged growth of serologically distinct mouse type C RNA viruses in human cells were previously shown to have acquired common envelope properties distinct from those of either parental virus (Kirsten and Rauscher murine leukemia viruses). Virus neutralization tests show that the viruses selected in human cells possess envelope antigens identical to those of endogenous type C viruses of BALB/c and NIH Swiss mouse cells in which the parental viruses had been propagated. In contrast, the p12 polypeptide of each virus selected in human cells is antigenically indistinguishable from that of its respective parental virus, and different from those of known endogenous mouse type C viruses. Molecular hybridization indicates significant differences in the genetic sequences of the Kirsten murine leukemia virus isolate and its parent, excluding the possibility that it arose from a point mutation. These findings indicate that the viruses selected in human cells represent genetic recombinants between exogenous and endogenous mouse type C viruses.

- 2031 A PROPOSED NOMENCLATURE FOR THE VIRION PROTEINS OF ONCOGENIC RNA VIRUSES. (E.) August, J. T. (Albert Einstein Coll. Med., Bronx, N.Y.), D. P. Bolognesi, E. Fleissner, R. V. Gilden and R. C. Nowinski. *Virology* 60:595-601, 1974.

Conventions proposed and agreed upon for designating viral proteins at a meeting of approximately 50 active investigators in the field are described. It is suggested that the viral proteins be designated according to their apparent molecular wt in thousands. Proteins should be designated by a lower case 'p' and glycoprotein by a 'gp' placed before the number indicating the molecular wt. Where the content leaves any ambiguity about the virus of origin, the name of the virus from which the protein is derived may be prefixed to the protein designation, such as MuLV p30 to indicate the murine leukemia virus protein of molecular wt 30,000. It is also proposed that when the antigenic determinants of a given protein are under consideration they be referred to in relation to the common nomenclature of type-specific, group-specific, and interspecies, such as p30 *type*, p30 *group*, or p30 *interspecies*. Additional information concerning the structural role of a protein or its properties may be added in parentheses at the investigator's discretion. The advantages and disadvantages of this nomenclature system are discussed.

- 2032 THE EFFECT OF GROWTH CONDITIONS ON NAD^+ AND NADH CONCENTRATIONS AND THE $\text{NAD}^+:\text{NADH}$ RATIO IN NORMAL AND TRANSFORMED FIBROBLASTS. (E.) Schwartz, J. P. (Nat'l. Inst. Neurological Dis. Stroke, Bethesda, Md.), J. V. Passonneau, G. S. Johnson and I. Pastan. *J Biol Chem* 249(13):4138-4143, 1974.

The total NAD^+ and NADH concentrations were measured and the $\text{NAD}^+:\text{NADH}$ ratio calculated for 3T3 fibroblasts, simian virus 40 (SV40) transformed 3T3 cells, normal rat kidney fibroblasts, and the murine sarcoma virus (Kirsten strain) transformed normal rat kidney fibroblasts. The absolute levels decreased 2- to 3-fold with transformation. The $\text{NAD}^+:\text{NADH}$ ratio in the normal cells ranged from 3.1 to 3.6, and increased 3- to 4-fold as they grew from logarithmic to stationary phase. The final ratio was a direct function of the final cell density achieved for the 3T3 cells. In contrast, the $\text{NAD}^+:\text{NADH}$ ratio of the transformed cells was low (1.2 to 3.2) and did not rise when the cells reached a high density. Comparable results were obtained for the ratio of free $\text{NAD}^+:\text{NADH}$. This ratio was determined by analyzing the cellular pyruvate and lactate concentrations and calculated using the K_{eq} of lactate dehydrogenase. Attempts to alter the ratio by treatment of the cells with agents capable of elevating the intracellular cyclic adenosine 3':5'-monophosphate levels were unsuccessful. Nor did serum deprivation or agents capable of lowering the cyclic adenosine 3':5'-monophosphate levels affect the $\text{NAD}^+:\text{NADH}$ ratio. The inability of cells to elevate their $\text{NAD}^+:\text{NADH}$ ratio at confluency appears to be a characteristic of transformed cells and related to their defective growth control.

- 2033 POSTTRANSCRIPTIONAL BLOCK TO ADENOVIRUS REPLICATION IN NONPERMISSIVE MONKEY CELLS. (E.) Fox, R. I. (Albert Einstein Coll. Med., Bronx, N.Y.) and S. G. Baum. *Virology* 60(1):45-53, 1974.

Events occurring during the abortive infection of CV-1 monkey cells by human adenoviruses were compared with those occurring during the complete replicative cycle which results from adenovirus and simian virus 40 (SV40) coinfection of these cells. In light of previous data indicating that replication in the former is blocked at a posttranscriptional event, two of the known posttranscriptional events were studied: attachment of polyadenylic acid to mRNA; and attachment of mRNA to ribosomes. The attachment of poly(A) to adenovirus mRNA during permissive and nonpermissive infection did not differ. Polyribosomal fractions of adenovirus-infected monkey cells contained adenovirus-specific RNA in the presence and absence of SV40 coinfection; however, in the presence of SV40 coinfection, more RNA hybridizable to adenovirus 7 DNA, was present. Furthermore, analysis of polyribosome-associated RNA revealed that "enhanced" polyribosomes were associated with both "early" and "late" adenovirus RNA, whereas polyribosomes from unenhanced infection showed a relative paucity of "late" mRNA. Thus, the block to efficient replication of human adenoviruses in monkey cells appears to occur at a posttranscriptional level. In "unenhanced" infection, the attach-

ment of late mRNA sequences to polyribosomes may be defective, although these sequences are synthesized and undergo addition of polyadenylic acid. This defective association of mRNA with polyribosomes may then lead to deficient translation of late viral proteins and thereby to a reduction in infectious virus.

- 2034 ENHANCEMENT OF ADENOVIRUS TRANSFORMATION BY TREATMENT OF HAMSTER EMBRYO CELLS WITH DIVERSE CHEMICAL CARCINOGENS. (E.) Casto, B. C. (BioLabs, Inc., Northbrook, Ill.), W. J. Pieczynski and J. A. DiPaolo. *Cancer Res* 34(1):72-78, 1974.

Primary hamster embryo cells were treated with various chemical carcinogens before, or after, inoculation with simian adenovirus 7. The viral transformation frequency was increased from 3- to 10-fold by treatment with methyl methanesulfonate, methyl-azoxymethanol acetate, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, and *N*-acetoxy-acetylaminofluorene; but no increase was demonstrated when cells were treated with *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, or 2-acetylaminofluorene. The frequency of viral transformation increased linearly with chemical concentration until a maximum level was reached; however, higher concentrations decreased the transformation frequency relative to that observed with lower doses. The ability of chemical carcinogens to enhance adenovirus transformation was correlated with their capacity to induce cell DNA lesions. This suggests that the increased transformation was due to an increased number of sites for attachment of viral DNA in regions of cell DNA strand breaks and subsequent repair synthesis, or in sites created by unrepaired DNA lesions during scheduled DNA synthesis.

- 2035 RESCUE OF SIMIAN VIRUS 40 (SV40) FROM SV40-TRANSFORMED CELLS BY FUSION WITH ANUCLEATE MONKEY CELLS AND VARIATION IN THE YIELD OF VIRUS RESCUED BY FUSION WITH REPLICATING OR NONREPLICATING MONKEY CELLS. (E.) Poste, G. (Roswell Park Mem. Inst., Buffalo, N.Y.), B. Schaeffer, P. Reeve and D. J. Alexander. *Virology* 60(1):85-95, 1974.

The rescue of infective simian virus 40 (SV40) from SV40-transformed mouse 3T3 (SV3T3) cells was studied after fusion with African green monkey kidney cells which had been enucleated by cytochalasin B treatment. The formation of heterokaryons by fusion of these two cell lines permitted the rescue of infective SV40, indicating that the rescue process does not require the participation of a functional permissive cell nucleus in the heterokaryon. The fusion of SV3T3 cells with permissive cells obtained from nondividing confluent stationary phase cell populations resulted in the rescue of a significantly higher titer of SV40 than that obtained from heterokaryons between similar SV3T3 cells and permissive cells harvested from replicating subconfluent log phase cultures; this effect was found with both anucleate and nucleated monkey cells. Thus, the physiological state of the permissive cells exerts

a direct effect on the amount of virus rescued from the heterokaryons. The mechanism by which the rate of division of the permissive cells used in heterokaryon formation might influence the yield of rescued SV40 is not clear.

- 2036 RESCUE OF DEFECTIVE SV40 FROM A TRANSFORMED MOUSE 3T3 CELL LINE: SELECTION OF A SPECIFIC DEFECTIVE. (E.) Yoshiike, K. (Nat'l. Inst. Hlth., Tokyo, Japan), A. Furuno and S. Uchida. *Virology* 60(2):342-352, 1974.

Small-plaque type simian virus 40 (SV40) yields various defectives containing deletions, insertions, and substitutions. To select a specific defective lacking a part of the late genes, the rescue of a defective mutant from a transformed mouse cell line was attempted. A triple heterokaryon culture was prepared consisting of monkey cells, 3T3 cells transformed by defective SV40, and 3T3 cells transformed by large-plaque type SV40 that yields no defective virus having the capability to direct T antigen synthesis. Virus recovered from the heterokaryon culture was propagated in monkey cells, and defective light virions were concentrated by CsCl equilibrium centrifugation. The virions and their DNA thus obtained were found to direct T antigen synthesis but not synthesis of virion antigen. Heteroduplex DNA molecules presumably consisting of a complete and a defective strand had mostly two single-stranded loops. The rescued defective SV40 genome appeared to have a deletion and an insertion at two separate and fixed sites.

- 2037 SURFACE BIOCHEMICAL CHANGES ACCOMPANYING PRIMARY INFECTION WITH ROUS SARCOMA VIRUS. II. PROTEOLYTIC AND GLYCOSIDASE ACTIVITY AND SUBLETHAL AUTOLYSIS. (E.) Bosmann, H. B. (U. Rochester, Sch. Med. Dent., N.Y.), T. Lockwood and H. R. Morgan. *Exp Cell Res* 83(1):25-30, 1974.

Normal chick embryo fibroblasts (CEF) were found to have low levels (<10 nmoles/10⁶ cells/hr) of β -fucosidase and α -mannosidase activity, intermediate levels (<50 nmoles/10⁶ cells/hr) of *N*-acetyl- β -galactosaminidase and β -galactosidase, and high levels (<100 nmoles/10⁶ cells/hr) of *N*-acetyl- β -glucosaminidase and acid phosphatase. High levels of pH 3.4 protease and low levels of pH 7.4 protease were also found. CEF infected and transformed with the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) had elevated levels of β -galactosidase, β -fucosidase, *N*-acetylglucosaminidase, *N*-acetylgalactosaminidase, and α -mannosidase activity; the acid phosphatase activity was not elevated. Proteolytic activity at pH 3.4 (cathepsin-like activity) was greatly elevated in the SR-RSV-CEF, while proteolytic activity at pH 7.4 (trypsin-like activity) was slightly lower than in normal CEF. Elevated levels of these degradative enzymes were not found in cells infected with leukosis virus (RAV-1). Similarly, with a temperature-sensitive mutant of SR-RSV (TS-68), the elevations in the activity of the degradative

enzymes occurred only at the permissive temperature. The observed elevations in the activities of the degradative enzymes may function for sublethal autolysis or the maintenance of the neoplastic state.

- 2038 ROSETTE-FORMING HUMAN LYMPHOID CELL LINE (T-CELL LINE MOLT). II. ABILITY FOR CLONAL GROWTH. (E.) Itoh, U. (Roswell Pk. Mem. Inst., Buffalo, N.Y.), J. Minowada, G. E. Moore and D. Pressman. *J Natl Cancer Inst* 52(5):1403-1407, 1974.

The colony-forming efficiency of the MOLT-4 cell line (a lymphoid cell line established from the peripheral blood of a patient with acute lymphoblastic leukemia) was studied using liquid medium and 0.3 and 0.15% agar medium. The cloning efficiency of MOLT-4 was compared with that of two lymphoblastoid cell lines having B-cell characteristics: B35M, which was derived from a biopsy specimen of Burkitt's lymphoma and was regarded as a malignant cell line; and B411-4, which was derived from the peripheral blood of a normal individual and was regarded as a "normal" cell line. The plating efficiency of MOLT-4 in liquid medium (1.5-1.7%) was the same as that of B411-4, while that of B35M was much greater (19.1-44.4%). The cloning efficiencies of MOLT-4 and B35M in soft agar medium were in the range 8-10% and 26-31%, respectively, while that of B411-4 was only 0.1-0.2%. This indicates that MOLT-4 cells may be malignant.

- 2039 HYBRIDIZATION OF SIMIAN VIRUS 40 COMPLEMENTARY RNA WITH NUCLEOLUS-ASSOCIATED DNA ISOLATED FROM SIMIAN VIRUS 40-TRANSFORMED CHINESE HAMSTER CELLS. (E.) Hirai, K. (Wistar Inst., Philadelphia, Pa.), D. Henner and V. Defendi. *Virology* 60(2):588-591, 1974.

Nucleolus-associated DNA was isolated from simian virus 40 (SV40)-transformed Chinese hamster cell lines, and was hybridized with SV40 [³H]cRNA to determine whether a unique integration site could be selectively fractionated between nucleoli and total nuclear DNA. The distribution pattern of integrated SV40 genomes between these two DNA fractions varied from clone to clone. These results are consistent with the hypothesis that there are multiple sites of integration of SV40 genomes into the DNA of Chinese hamster cells, but they do not rule out the possibility that integration at a unique site is required for transformation of the host cell.

- 2040 *IN VITRO* SYNTHESIS OF ROUS SARCOMA VIRUS-SPECIFIC RNA IS CATALYZED BY A DNA-DEPENDENT RNA POLYMERASE. (E.) Rymo, L. (Inst. Mol. Biol., U. Zurich, Switzerland), J. T. Parsons, J. M. Coffin and C. Weissmann. *Proc Natl Acad Sci USA* 71(7):2782-2786, 1974.

Synthesis of Rous sarcoma virus RNA was examined *in*

vitro with a new assay for radioactive virus-specific RNA. Nuclei from infected and uninfected chicken fibroblast cells were incubated with ribonucleoside [α -³²P]triphosphates, Mn⁺⁺, Mg⁺⁺ and (NH₄)₂SO₄. Incorporation into total and viral RNA proceeded with similar kinetics for up to 25 min at 37°. About 0.5% of the RNA synthesized by the infected system was scored as virus-specific, compared with 0.03% of the RNA from the uninfected system and 0.005% of the RNA synthesized by monkey kidney cell nuclei. Preincubation with DNase or actinomycin D completely suppressed total and virus-specific RNA synthesis. α -Amanitine, a specific inhibitor of eukaryotic RNA polymerase II, completely inhibited virus-specific RNA synthesis, while reducing total RNA synthesis by only 50%. It is concluded that tumor virus-specific RNA is synthesized on a DNA template, most probably by the host's RNA polymerase II.

- 2041 SIMIAN VIRUS 40 STRUCTURAL PROTEINS: AMINO-TERMINAL SEQUENCE OF THE MAJOR CAPSID PROTEIN. (E.) Lazarides, E. (Cold Spring Harbor Lab., N.Y.), J. G. Files and K. Weber. *Virology* 60(2):584-587, 1974.

The two major capsid proteins (VP1 and VP3) of simian virus 40 (SV40) were purified to homogeneity by electrophoresis in sodium dodecyl sulfate polyacrylamide gels. The amino-terminal sequence of VP1 (molecular wt 48,000) was found to be Ala-Pro-Thr-Lys-Arg-Lys-Gly-. No amino-terminal residue was found for VP3 (molecular wt 30,000); this capsid polypeptide may, therefore, have a blocked amino terminus.

- 2042 BIOGENESIS OF MAREK'S DISEASE (TYPE II LEUKOSIS) VIRUS *IN VITRO*: ELECTRON MICROSCOPY AND IMMUNOLOGICAL STUDY. (E.) Hamdy, F. (Dept. Vet. Animal Sci., U. Massachusetts, Amherst), M. Sevoian and S. C. Holt. *Infect Immun* 9(4):740-749, 1974.

The kinetic events involved in Marek's disease herpesvirus infection of avian cell culture were investigated by assaying viral infectivity and antigenicity as well as by electron microscopy during the infectious cycle. The levels of viral infectivity and complement-fixing (CF) antigens revealed that the rates of appearance of infectious particles and CF antigens were not synchronous. Viral specific CF antigen could be detected 5 hr after infection, whereas viral infectivity or the appearance of viral particles could be demonstrated only after 10 hr of infection. High proportions of the recovered CF antigens during the various stages of the infectious cycle were found to be soluble and did not sediment with the virus particles. Cytological analysis of the developmental stages of the JM virus-infected cells by thin sectioning and electron microscopy revealed that at 8 hr small particles approximately 35 nm in diameter appeared in the cell nuclei. The appearance of nucleocapsids occurred at 10 hr, and these were of varying shapes; however, all were approximately 100 nm in diameter. At approximately 18

hr postinfection, mature virus particles were observed. Viral maturation of the immature particles occurred by the acquisition of envelope from the inner leaflet of the nuclear membrane or from the cytoplasmic membrane of the cell.

2043 RESCUE OF DEFECTIVE SV40 FROM MOUSE-HUMAN HYBRID CELLS CONTAINING HUMAN CHROMOSOME 7.

(E.) Croce, C. M. (Wistar Inst. Anat. Biol., Philadelphia, Pa.), K. Huebner, A. J. Girardi and H. Koprowski. *Virology* 60(1):276-281, 1974.

Subcloning of simian virus 40 (SV40) T-antigen positive, V-antigen negative hybrid clones derived from the fusion of mouse thymidine kinase-deficient Cl-1D cells and SV40-transformed human cells (LNSV) resulted in their segregation into T-antigen positive and negative subclones which still contained the full complement of mouse chromosomes. These subclones were analyzed for SV40 V-antigen and virion formation after fusion of the subclone cells with African green monkey kidney (CV-1) cells. All subclones which contained the human chromosome 7 showed the presence of V-antigen in the heterokaryocytes after fusion with CV-1 cells; all subclones which had lost human chromosome 7 failed to express V-antigen following fusion with CV-1 cells. Wild-type plaque-forming SV40 could not be rescued from any of the T-antigen positive, or negative clones or subclones, but defective SV40 virions were rescued from a hybrid subclone in which the only human chromosome present was chromosome 7; two subclones which had lost human chromosome 7 showed no SV40 virion formation. Thus, the SV40 genome appears to be integrated in human chromosome 7; if any part of the SV40 genome is integrated in other human chromosomes, it apparently cannot express any of its functions.

2044 RNA TUMOR VIRUSES OF PHEASANTS: CHARACTERIZATION OF AVIAN LEUKOSIS SUBGROUPS F AND G.

(E.) Fujita, D. J. (U. Southern California, Sch. Med., Los Angeles), Y. C. Chen, R. R. Friis and P. K. Vogt. *Virology* 60(2):558-571, 1974.

Endogenous leukosis-like viruses of ring-necked pheasants (*Phasianus colchicus*) and golden pheasants (*Chrysolophus pictus*) have been isolated and characterized. The majority of the normal pheasant embryo cultures contain helper activity for the defective Bryan high titer strain of Rous sarcoma virus, apparently reflecting the presence of leukosis virus genetic information in pheasants. The Rous sarcoma pseudotypes produced with endogenous helper activity from ring-necked pheasants belong to subgroup F. The pseudotypes from golden pheasant cells constitute subgroup G. Subgroup F and G pseudotypes can infect all known genetic types of chicken fibroblasts as well as pheasant and Japanese quail cells, but do not plate on goose cells. Duck cells are resistant to subgroup G but not to F. The subgroup F and G helper-viruses isolated from Rous sarcoma viral pseudotypes show interference with their homologous subgroup. RAV-61, a standard of subgroup F, interferes with pseudotypes produced with endogenous helper activity from ring-

necked pheasant cells but not with subgroup G pseudotypes. Subgroups F and G do not cross-react with subgroup A to E in neutralization tests. Some normal ring-necked pheasant sera have anti-F activity. Subgroup F and probably also G leukosis-like viruses can undergo genetic recombination with nondefective avian sarcoma viruses.

2045 THE CELLULAR BASIS OF IMMUNOSUPPRESSION CAUSED BY THE RADIATION LEUKAEMIA VIRUS.

(E.) Peled, A. (Dept. Chem. Immunol., Weizmann Inst. Sci., Rehovot, Israel) and N. Haran-Ghera. *Immunology* 26(2):323-329, 1974.

Infection of adult C57Bl/6 mice with the radiation leukemia virus (0.5 ml, i.p.) resulted in suppression of the ability of the animals to respond to an immunizing inoculum of sheep RBC. Results of transfer experiments indicated that the immunosuppressive effect was expressed at the immunocompetent cell level, and that the virus affected the thymus-derived population of immunocytes. The immunosuppressive effect of the virus on thymus cells, independent of any contribution by cells of bone marrow origin, was verified with thymus-independent immunogens, polyvinylpyrrolidone (PVP) or pneumococcal polysaccharide SIII (PPS). Mice inoculated with the radiation leukemia virus produced nearly normal amounts of plaque-forming cells producing antibodies against PVP and PPS, thereby confirming that the immunosuppressive effect of the radiation leukemia virus was on thymus-derived cells.

2046 EXPERIMENTAL STUDIES ON THE SABIN-FELDMAN TEST IN VIRAL MURINE LEUKEMIAS. (Ger.)

Alexander, M. (Westend Clin., Free U., Berlin, Germany) and S. Jelen. *Verh Dtsch Ges Inn Med* 78:120-122, 1972.

Since it has recently been found that a large number of patients with hemoblastosis have positive Sabin-Feldman tests with high titers but no evidence of toxoplasmosis at autopsy, experiments were performed on mice to determine whether murine leukemia had any effect on this test. No positive Sabin-Feldman tests were obtained on serum from any of 46 female and 48 male BALB/c mice which developed leukemia after inoculation with Rauscher virus. All of these mice initially had negative tests before inoculation. Tests were performed 9-10 days and between the 21st and 30th day after inoculation. Negative Sabin-Feldman tests were also obtained on serum from 38 toxoplasmosis-free mice of the Groppe strain which developed leukemia after inoculation with Friend's virus, in 10 Agnes Bluhm mice with Graffi's leukemia, and in 38 BALB/c mice which developed Graffi's leukemia after i.p. injection of homogenized lymph node and thymus suspensions from Agnes Bluhm mice with Graffi's leukemia. The high incidence of positive Sabin-Feldman tests in human hemoblastosis may be due to increased susceptibility of lymph nodes inflamed by toxoplasmosis to undergo malignant transformation. It is also possible that positive tests might have been due to passive transmission of antibodies by

blood transfusion, although these antibodies would be present at low titers and would not be detected after a few weeks. Changes in γ -globulins could also result in positive tests for toxoplasmosis.

2047 TRANSFER OF CHROMOSOMAL MATERIAL: ASSOCIATION OF RESCUABLE SARCOMA VIRUS GENOME WITH THE CHROMOSOMAL FRACTION. (E.) Ebina, T. (Wistar Inst., Philadelphia, Pa.), R. Miao and Y. Watanabe. *Exp Cell Res* 88(1):203-206, 1974.

Trypsinized primary Syrian hamster embryo cells were mixed with metaphase chromosomes isolated from hamster HT-1 cells (a line cryptically transformed by Moloney murine sarcoma virus (MSV) which produces neither infectious virus nor the group-specific antigen of murine C-type RNA viruses). Twenty-four hr later, the cells were again exposed to chromosomes. No foci developed in the cultures within 30 days. When chromosome-treated hamster embryo cells were trypsinized 10 days after treatment and cocultivated with Rauscher murine leukemia virus-producing NIH-3T3 cells (RLV-3T3), sarcoma virus was recovered regularly. A small number of foci were also obtained on assay of cocultivation fluids from chromosome-treated HT-1 cells and Rauscher-3T3 cells (HE-(HT-1)). No sarcoma virus was recovered after cocultivation of Rauscher-3T3 cells and control hamster embryo cells. The data suggest that the chromosomes or chromosome-associated factor(s) of HT-1 cells carry the rescuable MSV genome but that the uptake of the chromosome-associated MSV genome into hamster embryo cells is not sufficient for transformation.

2048 THE INFIDELITY OF AVIAN MYELOBLASTOSIS VIRUS DEOXYRIBONUCLEIC ACID POLYMERASE IN POLYNUCLEOTIDE REPLICATION. (E.) Battula, N. (Inst. Cancer Res., Philadelphia, Pa.) and L. A. Loeb. *J Biol Chem* 249(13):4086-4093, 1974.

The accuracy by which purified avian myeloblastosis virus (AMV) DNA polymerase can copy a variety of synthetic polynucleotide templates was investigated *in vitro*. When copying ribopolynucleotide and deoxyribopolynucleotide templates, the frequency of error was about 1 in 600 when copying homopolymer templates and about 1 in 6000 when copying alternating copolymer templates. The product of the reaction was analyzed by velocity sedimentation and equilibrium density gradient centrifugation. The results indicate that the entire length of the given template was copied, the incorrectly base-paired nucleotides were an integral part of the polynucleotide product, and these errors were randomly distributed. Polyacrylamide gel electrophoretic analysis of the purified polymerase showed two subunits, α and β . The incorporation of the correct and incorrect nucleotides catalyzed by the active α subunit was not influenced by the inactive β subunit. The purified polymerase had no detectable exo- or endodeoxyribonuclease activity. AMV DNA polymerase exhibited identical requirements for the incorporation of the correct and incorrect nucleotides. The

error rate was not a function of the number of initiator termini, Mg^{2+} concentration, time of incubation or amount of enzyme. It was dependent on the type of template and on the ratio of correct to incorrect nucleotides in the reaction mixture. If the DNA polymerase from AMV makes similar errors *in vivo*, this enzyme may be mutagenic.

2049 ANTIBODY TO LEUKEMIA VIRUS: WIDESPREAD OCCURRENCE IN INBRED MICE. (E.) Nowinski, R. C. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and S. L. Kaehler. *Science* 185(4154):869-871, 1974.

Studies that substantiate the view that the mouse is immunologically competent with respect to its endogenous leukemia virus (MuLV) are presented. With a sensitive radioimmune precipitation (RIP) assay, immunoglobulin (IgG) antibody to MuLV was found in mice of virtually all inbred mouse strains. These findings indicate that immune responsiveness of the mouse to MuLV might be the rule, rather than the exception. The nature of the immunoglobulins in mouse serum to MuLV was examined further by the use of monospecific antibodies to mouse immunoglobulins. It was found that mouse antibodies to MuLV were distributed among all four classes of immunoglobulins (IgG₁, IgG₂, IgM, and IgA). In most cases, the highest titer antibodies were of the IgG₁ and IgG₂ classes. The detection of antibody to virus both in mice of nonproducer (low leukemic) strains as well as producer (high leukemic) strains is of significance to human leukemia, where it is of interest to determine evidence of virus infection in the absence of overt virion production.

2050 CONTROL OF INTERFERON, MIGRATION INHIBITION FACTOR, AND EXPRESSION OF VIRUS CAPSID ANTIGENS IN BURKITT'S LYMPHOMA-DERIVED CELL LINES: ROLE OF L-ARGININE. (E.) Archer, D. L. (Dept. Microbiol., U. Maryland, College Park) and B. G. Young. *Infect Immun* 9(4):684-689, 1974.

The effects of an arginine-utilizing mycoplasma, *Mycoplasma arginini*, and of varying levels of arginine in the growth media of the Epstein-Barr virus (EBV)-containing EB1 and EB3 cell lines, and the EBV-free RPMI 1788 cell line, were studied. L-Arginine, at a concentration of 0.1 mM in the growth medium, led to a reduction of the EBV capsid antigen content of the EB1 and EB3 cell lines as determined by indirect immunofluorescence, and *M. arginini* infection enhanced this reduction. The synthesis of two immune products, interferon and macrophage migration inhibition factor, was enhanced by growing the cell lines in medium containing arginine at a concentration of 0.1 mM, but the RPMI 1788 cell line produced much less of both products than EB1 or EB3 under these conditions. Infection of the cell lines with *M. arginini* reduced the amount of interferon produced and completely inhibited macrophage migration inhibition factor synthesis. The addition of arginine to a final concentration of 0.6 mM in the growth medium caused a dual effect: the EB1 and

EB3 cell lines maintained the original level of EBV capsid antigens, even when infected with *M. arginini*; immune product synthesis was greatly reduced or completely inhibited by the addition of arginine, and *M. arginini* infection caused no further reduction of immune product synthesis.

- 2051 T LYMPHOBLASTOID CELL LINES FROM MAREK'S DISEASE LYMPHOMAS. (E.) Powell, P. C. (Houghton Poultry Res. Station, Huntington, England), L. N. Payne, J. A. Frazier and M. Rennie. *Nature* 251(5470):79-80, 1974.

The establishment of two cell lines from Marek's disease (MD) lymphomas and their characterization as T cells are reported. Ovarian lymphomas were collected from experimentally infected birds at about 5 wk of age. Single cell suspensions were prepared, adjusted to 5×10^6 cells/ml, and cultures of 5 ml volume incubated in screw cap glass universal bottles at either 37 or 40 C. Cultures of lymphocytes separated from heparinized blood samples were initiated in a similar way. Two cultures were found to be growing free floating cells, one 31 days after initiation (HPRS Line 1) and the other 92 days after initiation (HPRS Line 2). Line 1 cells stained for T-surface determinants, showing smooth membrane staining with capping, typical of T cells. When examined for membrane fluorescence, 100% of line 2 cells stained for T-cell determinants. The identification of the cell lines as T cells is supported by the ultrastructural studies which showed the presence of abundant ribosomes and sparse endoplasmic reticulum.

- 2052 THE MAPPING AND ORDERING OF FRAGMENTS OF SV40 DNA PRODUCED BY RESTRICTION ENDONUCLEASES. (E.) Subramanian, K. N. (Yale U. Sch. Med., New Haven, Conn.), J. Pan, S. Zain and S. M. Weissman. *Nucleic Acids Res* 1(6):727-752, 1974.

Simian virus 40 (SV40) DNA is cleaved by the *Escherichia coli* bearing resistance transfactor II and *Haemophilus aegyptius* restriction endonucleases to give rise to two different sets of 16 fragments each. These fragments were ordered by analysis of the products of redigestion of one set of fragments with another restriction enzyme. The cleavage sites were mapped based on length measurements of the products of each cleavage. This provides a convenient group of small DNA fragments suitable for sequence analysis investigation of the transcripts present in infected cells, or construction of deletion substitution variants of the virus.

- 2053 FORMATION AND BIOLOGIC ROLE OF POLYOMA VIRUS-ANTIBODY COMPLEXES. A CRITICAL ROLE FOR COMPLEMENT. (E.) Oldstone, M. B. A. (Scripps Clin. Res. Fdn., La Jolla, Calif.), N. R. Cooper and D. L. Larson. *J Exp Med* 140(2):549-565, 1974.

Interaction of polyoma virus, specific antibody, and complement (C) was studied. Evidence was gathered

that C1 through C3 and not C5 through C9 enhance neutralization of virus-antiviral antibody (V-Ab) complexes. Complement enhancement of neutralization occurs primarily by agglutination of V-Ab complexes and not by virion lysis or attachment of large protein molecules to the V-Ab complex. In this model, binding of C1, 4, 2, 3 to the V-Ab complex may explain why some viruses concentrate in or infect certain cells bearing C3 receptors such as B lymphocytes, macrophages, and monocytes.

- 2054 AN EXTRA SPECIES OF LYSINE TRANSFER RIBONUCLEIC ACID IN POLYOMA VIRUS-TRANSFORMED CELLS IN TISSUE CULTURE. (E.) Jacobson, E. L. (Dept. Biochem., Kansas State U., Manhattan), H. Juarez, C. Hedgcoth and R. A. Consigli. *Arch Biochem Biophys* 163(2):666-670, 1974.

Isoaccepting tRNAs from various mouse cells were fractionated on columns of benzoylated DEAE cellulose. Lysine tRNA from mouse embryo, adult mouse liver and kidney, primary mouse embryo cells in tissue culture, and an established tissue culture line of mouse fibroblasts (3T3) has two peaks of isoaccepting tRNA; lysine tRNA from two established lines of polyoma virus-transformed cells contains an additional peak of lysine tRNA. The extra peak in transformed cells comprises about 25% of the acceptor capacity for lysine. It is stable to denaturation and re-naturation and can be chromatographed, stripped of lysine, recharged, and rechromatographed. The extra peak is present in tRNA from transformed cells and absent in tRNA from normal cells regardless of whether the lysyl-tRNA ligase used for aminoacylation is from normal or transformed cells. Isoaccepting tRNAs for arginine, leucine, serine, valine, histidine, and tyrosine reveal similar profiles for the various tRNAs from normal and transformed cells.

- 2055 EPSTEIN-BARR VIRUS: ONE OR A FAMILY OF VIRUSES. (E.) Pearson, G. R. (Nat'l. Cancer Inst., Bethesda, Md.). *Cancer Res* 34(5):1237-1240, 1974.

Immunofluorescence tests on acetone-fixed smears and viable cell suspensions of Epstein-Barr virus (EBV)-producing lymphoblastoid cell lines have been used extensively for screening sera for antibodies to EBV-associated antigens. Of these tests, the anti-VCA (viral capsid antigen) test has yielded no results that might implicate different subtypes of EBV associated with different disease categories; the anti-EA (early antigens) tests have yielded results which might or might not suggest the involvement of different subtypes of EBV in infectious mononucleosis (IM), nasopharyngeal carcinoma (NPC), and Burkitt's lymphoma (BL); and the membrane immunofluorescence test has failed to identify disease-specific membrane antigen components indicative of a family of related but distinct herpesviruses in the causation of these diseases. Preliminary neutralization kinetic experiments have also failed to demonstrate a difference in the neutralizing activity of sera from different disease categories. Investiga-

tions on cell lines of different origin have used a variety of immunological methods; the results have indicated possible antigenic differences in cell lines derived from BL, NPC, and IM, but have shown no differences in reactivity patterns with sera from patients with different EBV-associated diseases. Thus, at this time, there is no clear evidence for or against the existence of a family of related herpesviruses with different biological activities.

- 2056 TRANSCRIPTION OF HETEROPOLYMERIC REGIONS OF AVIAN MYELOBLASTOSIS VIRUS HIGH MOLECULAR WEIGHT RNA WITH *ESCHERICHIA COLI* DNA POLYMERASE I. (E.) Sarin, P. S. (Nat'l. Cancer Inst., Bethesda, Md.), M. S. Reitz and R. C. Gallo. *Biochem Biophys Res Commun* 59(1):202-214, 1974.

High concentrations of a purified preparation of *Escherichia coli* DNA polymerase I were able to transcribe heteropolymeric regions of the avian myeloblastosis virus high-molecular wt RNA, both in the presence and absence of oligo (dT) as a primer. Some of the DNA transcripts specifically hybridized to avian myeloblastosis virus high-molecular wt RNA, the size of the DNA transcript being approximately 5S. In contrast to the reverse transcriptase from RNA tumor viruses and human acute leukemic cells, the transcription of poly(A) regions of the viral high-molecular wt RNA into poly (dT) and poly (dA) was 5- to 40-fold greater than the transcription of heteropolymeric regions of this RNA. *E. coli* DNA polymerase was 10- to 200-fold less efficient in transcribing heteropolymeric regions of the avian myeloblastosis virus high-molecular wt RNA relative to activated salmon sperm DNA than DNA polymerases from avian myeloblastosis virus, mammalian type-C viruses, and human acute leukemic cells.

- 2057 THE VIRAL DNA REPLICATION COMPLEX OF ADENOVIRUS 12. (E.) Shiroki, K. (Inst. Med. Sci., Tokyo, Japan), H. Shimojo and K. Yamaguchi. *Virology* 60(1):192-199, 1974.

Confluent monolayer cultures of resting human embryonic kidney (HEK) cells were infected with the prototype strain of adenovirus 12 (Ad 12). Viral DNA synthesis began to increase at 24 hr postinfection (p.i.) and reached a maximum at 32 hr p.i. Increases in viral RNA and total protein synthesis preceded viral DNA synthesis. HEK cells infected with ³²P-labeled Ad 12 virions for 32 hr were labeled with ³H-thymidine and the nuclei were isolated and treated by the M-band technique. Both parental and nascent DNAs were present in the M-band fraction. The M-band fraction from infected cells actively synthesizing viral DNA contained the viral DNA replication complex. The DNA synthesizing activity *in vitro* with isolated nuclei and the M-band fractions began to increase at 24 hr p.i. and reached a maximum at 32 hr p.i. The DNA synthesized *in vitro* was viral as revealed by DNA-DNA hybridization. Electron microscopic autoradiograms of infected cells revealed silver grains in association with band-like inclusion bodies in the interior of the nucleus; the silver grains did not associate with the nuclear

membrane. After chase for 1 hr, most of the grains were found in the same state. Thus, the viral DNA replication complex is formed in the interior of the nucleus and contained in the M-band after fractionation.

- 2058 SUSCEPTIBILITY OF XERODERMA PIGMENTOSUM CELLS TO CHROMOSOME BREAKAGE BY ADENOVIRUS TYPE 12. (E.) Stich, H. F. (Cancer Res. Ctr., U. British Columbia, Vancouver, Canada), W. Stich and P. Lam. *Nature* 250(5467):599-601, 1974.

To characterize the response of DNA repair-deficient cells toward carcinogens and mutagens, the effect of infectious and impaired human adenovirus type 12 (AD12) on cultured fibroblasts of three unrelated xeroderma pigmentosum (XP) patients and three control subjects was examined. Since the repair capacity of the three XP cultures varied, the study also explored whether different degrees of repair deficiency gave rise to different sensitivities towards the chromosome-damaging effect of infectious and UV-impaired AD12. Controls and XP cells seemed to differ in the extent of chromosome damage rather than in the type of chromosome aberrations which followed infection with nonirradiated or UV-irradiated AD12. Chromosome fragmentation occurred in the examined XP cells as well as in the controls. The repair of UV-irradiated viral genomes, and hence the restoration of replication and chromosome-damaging function, occur at lower levels in XP cells than in host cells with an unimpaired DNA repair system. The data also show that the chromosome-damaging function is more readily restored than the replicative capacity of the virus.

- 2059 INTERFERON PRODUCTION BY MACROPHAGES FROM ADULT AND NEWBORN RABBITS BEARING FIBROMA VIRUS-INDUCED TUMORS. (E.) Pathak, P. N. (Coll. Vet. Med., U. Illinois, Urbana) and W. A. F. Tompkins. *Infect Immun* 9(4):669-673, 1974.

Tumors were induced in adult and newborn rabbits by inoculation of fibroma virus (2.5×10^5 plaque-forming U; intradermally in adults, s.c. in newborns). After 10 to 14 days, oil-induced peritoneal macrophages were harvested, purified, and tested *in vitro* for interferon synthesis after stimulation with specific and nonspecific viruses. Peritoneal macrophages from adult rabbits that had initiated tumor regression produced high levels of interferon (titers of 160-640) after stimulation with fibroma virus, whereas macrophages from normal adult rabbits failed to produce significant levels of interferon under the same conditions (titers from <10 to 10). Furthermore, fibroma-immune macrophages responded to vaccinia virus and Newcastle disease virus with higher levels of interferon than did normal macrophages. In contrast, macrophages from newborn tumor-bearing rabbits that showed no evidence of tumor regression failed to respond to fibroma virus stimulation with higher levels of interferon (titer ranges from <10 to 10). These macrophages did, however, yield significantly more interferon than newborn control macrophages when stimulated with Newcastle disease virus (titers of 10-80). These data suggest that

interferon production may be an expression of macrophage activation to fibroma antigens and that macrophage activation is impaired in newborn rabbits with progressively growing tumors.

2060 HIGH SPECIFIC INFECTIVITY AVIAN RNA TUMOR VIRUSES. (E.) Smith, R. E. (Duke U. Med. Ctr., Durham, N.C.). *Virology* 60(2):543-547, 1974.

Conditions for obtaining avian RNA tumor viruses of high specific infectivity were investigated. The Prague strain of Rous sarcoma virus of subgroup C showed highest specific infectivity when harvested from virus-producing chick embryo fibroblasts at 20-min intervals. Such virus was five times more infectious than virus harvested at 30-sec intervals, and ten times more infectious than virus harvested at 24-hr intervals. Other cloned nondefective RNA tumor viruses showed similar patterns. Prompt chilling of virus collected at frequent intervals was essential because otherwise it was rapidly heat-inactivated. Virus harvested at 24-hr intervals was heat-inactivated much more slowly. This difference, however, was not due to differences in the virus particles, but to differences in media that had been in contact with cells for varying periods of time.

2061 CHICKEN CELL-FREE PROTEIN SYNTHESIZING SYSTEM PROGRAMMED BY ENDOGENOUS mRNA. REACTION CONDITIONS AND COMPARISON OF NORMAL AND TUMOUR SYSTEMS. (E.) Maly, A. (Lab. Biochem. Invest. Cancer, Czechoslovak Acad. Sci., Prague), J. Hradec and J. Riman. *Neoplasma* 21(4):395-400, 1974.

The optimal reaction conditions for protein synthesis in a cell-free protein synthesizing system containing ribosomes and soluble components isolated from normal chicken livers were determined. The optimal reaction conditions for cell-free protein synthesis directed by endogenous mRNA were: 3 mM Mg^{2+} , 55 mM NH_4Cl , and 2-3 mM guanosine 5'-triphosphate. Under the conditions used, 120 μ g of ribosomes were saturated by 40 μ g of supernatant protein and the reaction ceased after about 10 min. The normal chicken liver cell system was then compared with that prepared from leukemic chicken livers and leukemic chicken myeloblasts. There were no significant differences in the overall amount of peptides synthesized by the endogenous reaction in the leukemic and normal systems. Thus, the polysomal system appears to be universal, applying to both normal and cancer cells.

2062 HEMAGGLUTININATING ACTIVITY OF BOVINE PAPILLOMA VIRUS. (E.) Favre, M. (Gustave-Roussy Inst., Villejuif, France), F. Breitburd, O. Croissant and G. Orth. *Virology* 60(2):572-578, 1974.

Purified preparations of bovine papilloma virus (BPV) agglutinate C3H/He mouse erythrocytes. Maximal hemagglutination (HA) activity occurs at 4 C, between pH

6.8 and 8.4. The adsorbed virus is readily eluted at 37 C. The BPV receptors on mouse erythrocytes show a high resistance to receptor-destroying enzyme or influenza A2 neuraminidase. The BPV hemagglutinin is associated with both full and empty viral particles. Sera of animals infected with BPV contain high titers of antibodies inhibiting the HA reaction.

2063 INCOMPLETE PARTICLES OF ADENOVIRUS. I. CHARACTERISTICS OF THE DNA ASSOCIATED WITH INCOMPLETE ADENOVIRIONS OF TYPES 2 AND 12. (E.) Burlingham, B. T. (Div. Biol., Kansas State U., Manhattan), D. T. Brown and W. Doefler. *Virology* 60(2):419-430, 1974.

When KB or HeLa cells were infected with human adenovirus type 2 or 12, five discrete types of incomplete particles were produced in large quantity in addition to the complete infectious adenovirions. The incomplete particles could be purified by equilibrium centrifugation in CsCl density gradients. Each type of incomplete adenovirion had a unique buoyant density in CsCl and contained a specific sized fragment of adenovirus DNA. The incomplete adenovirions had a very low specific infectivity in human embryonic kidney cells as compared with that of the mature virion. Although other explanations cannot be excluded, this infectivity is likely to be due to a low level of contamination with complete virions.

2064 HERPESVIRUS AND EPSTEIN-BARR VIRUS ANTIBODIES AND CARCINOMA OF THE INTRINSIC LARYNX. (E.) Sessions, R. B. (Baylor Coll. Med., Houston, Tex.), H. Goepfert, E. Adam, and W. E. Rawls. *Arch Otolaryngol* 99(4):261-263, 1974.

Serum antibody levels for the herpesvirus types 1 and 2 and for the Epstein-Barr (EB) virus were analyzed in 39 laryngeal carcinoma patients and matched with those of 59 noncancer control patients. The incidence of heavy smoking was significantly higher in the cancer group than in the control group, as was the incidence of excessive alcohol consumption. The mean antibody titers to type 1 virus were significantly higher among blacks than whites, but did not differ between the cancer and control groups; similar results were found for antibody titers to type 2 virus. Neither the occurrence of EB antibodies nor the mean antibody titers differed significantly between the cancer and control groups. The data suggest that EB virus is not etiologically related to laryngeal cancer, but do not exclude the possibility that herpesvirus type 1 is etiologically related to laryngeal cancer.

2065 ANIMAL MODELS: HERPESVIRUS SAIMIRI, A NON-HUMAN PRIMATE MODEL FOR HERPESVIRUS-ASSOCIATED NEOPLASIA OF MAN. (E.) Ablashi, D. V. (Natl. Cancer Inst., Bethesda, Md.) and G. R. Pearson. *Cancer Res* 34(5):1232-1236, 1974.

Past and present evidence strongly indicates an association between the Epstein-Barr virus (EBV) and

Burkitt's lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma. Cell cultures of other than human origin can be successfully infected with EBV, and malignant lymphoma has occurred in cotton-top marmosets following inoculation of EBV propagated in marmoset cells. Reticuloproliferative disease has also been reported upon inoculation of EBV in an owl monkey. Although some data suggest a possible oncogenic role of EBV, further studies are needed for more conclusive evidence of this, especially to demonstrate that EBV harvested from human cells is tumorigenic. All evidence to date tends to relate *Herpesvirus saimiri* (HVS) to the etiology of a lymphoma and leukemia in monkeys. There are also a number of *in vivo* and *in vitro* similarities between HVS and EBV. HVS infection in the monkey appears to be an excellent animal model for investigation into the involvement of herpesvirus in the etiology of neoplasia; it can also be used as a definitive model for studying measures for preventing and treating human cancers.

- 2066 HUMAN CANCER VIRUS: ANOTHER CANDIDATE.
(E.) Anonymous. *Med World News* 15(30:20, 1974.

The announcement of a "prime candidate" human breast cancer virus by researchers at the Michigan Cancer Foundation of Detroit is reported. The virus, designated 734B, was isolated from a cell culture derived from a patient with breast carcinoma. The virus is scheduled to be distributed to six cancer research laboratories for confirmatory testing. Advances recently reported on another suspected human cancer virus, the transitional-cell cancer-associated virus, isolated by researchers at the University of Minnesota Medical School in Minneapolis, are also discussed. This virus was originally isolated from a patient with a primary papillary tumor of the renal pelvis and later found in additional papillary tumors. It is capable of causing malignant *in vitro* transformation of a variety of mammalian cells. Coincident with the transformation an antigen appears on the surface of these animal cells that is recognized by the serum and lymphocytes of patients with transitional-cell cancer.

- 2067 QUANTITATIVE STUDIES ON INTRACYTOPLASMIC A PARTICLES FORMED IN DNA/2 MOUSE LEUKEMIAS. (E.) Tsujimura, D. (Inst. Virus Res., Kyoto U., Japan) and H. Tanaka. *Cancer Res* 34(6):1475-1486, 1974.

Formation of intracytoplasmic A particles in DBA/2 mouse leukemias was studied with the fuchsin acid staining method. The A-particle index (API) was defined as the number of cells containing cytoplasmic aggregates of these particles/100 leukemia cells examined in lymph node smears. The following observations were made: (a) in 322 cases of spontaneous leukemias, API levels varied greatly from case to case, ranging from 0 to 80; (b) API was almost zero in mice that were nonleukemic; (c) during the natural course of leukemia, API rose significantly in almost one-half of the cases; (d) transplantation exerted a rather suppressive effect on API levels; (e) API's of thymus and leukemia cells circulating in peripheral blood were considerably different from those of lymph nodes; furthermore, (f) API was linearly related to the mitotic index of leukemia cells; and (g) as in interphase cells, usually a single A-particle aggregate was found in mitotic cells, which was transferred to one daughter cell, leaving the other A-particle free. These observations are discussed in connection with cell population kinetics of DBA/2 mouse leukemia cells.

2068 VIRUS TYPE-SPECIFIC THYMIDINE KINASE IN CELLS BIOCHEMICALLY TRANSFORMED BY HERPES SIMPLEX VIRUS TYPES 1 AND 2. (E.) Davis, D. B. (Roswell Park Mem. Inst., Buffalo, N.Y.), W. Munyon, R. Buchsbaum and R. Chawda. *J Virol* 13(1): 140-145, 1974.

The transformation of mouse cells (Ltk⁻) and human cells (HeLa Bu) from a thymidine kinase (TK)-minus to a TK⁺ phenotype (herpes simplex virus [HSV]-transformed cells) has been induced by infection with ultraviolet-irradiated HSV type 2, as well as by HSV type 1. Medium containing methotrexate, thymidine, adenine, guanosine, and glycine was used to select for cells able to utilize exogenous thymidine. The kinetics of thermal inactivation of TK from cells lytically infected with HSV type 1 or HSV type 2 and from HSV type 1- and HSV type 2-transformed cells have been determined. A 20-fold decrease in the TK activity of cell extracts from HSV type 2-transformed cells and Ltk⁻ cells lytically infected with HSV type 2 was produced after 3 hr of incubation at 41 C. These same conditions produce only a 2-fold decrease in the TK activities from HSV type 1-transformed cells and cells lytically infected with HSV type 1. These findings support the hypothesis that an HSV structural gene coding for TK has been incorporated in the HSV-transformed cells.

- 2069 A COMPARATIVE STUDY OF SV40-TRANSFORMED FIBROBLAST PLASMA MEMBRANE PROTEINS LABELLED BY ENZYMATIC IODINATION OR WITH TRINITROBENZENE SULFONATE. (E.) Vidal, R. (C.N.R. Ctr. Cytopharmacol., Torino, Italy), G. Tarone, F. Peroni and P. M. Comoglio. *FEBS Lett* 47(1):107-112, 1974.

Surface membrane proteins from simian virus 40 (SV40)-transformed mouse 3T3 fibroblasts were selectively labeled with trinitrobenzene sulfonate or labeled by lactoperoxidase-catalyzed iodination. The labeled proteins were purified and then separated by acrylamide gel electrophoresis. Labeling with enzymatic iodination gave an electrophoretic pattern of 20-25 different protein peaks, distributed along the entire gel length, indicating an extensive molecular wt range. Surface labeling with trinitrobenzene sulfonate gave a simpler pattern with 7-9 protein peaks. Proteins of intermediate wt labeled by enzymatic iodination were missed with the latter method. The fact that trinitrobenzene sulfonate labeled fewer membrane proteins may be attributable to the fact that it does not penetrate the outer surface molecular layer of the plas-

ma membranes as deeply as free iodine and/or to the fact that it binds protein amino groups more slowly than iodine binds with tyrosyl residues. However, the simplicity of the trinitrobenzene sulfonate labeling pattern makes this method extremely useful for the study of plasma membranes.

- 2070 RELATION OF TYPE 2 HERPESVIRUS ANTIBODIES TO CERVICAL NEOPLASIA: BARBADOS, WEST INDIES, 1971. (E.) Ory, H. (U.S. Dept. Hlth. Education Welfare, Ctr. Dis. Control, Atlanta, Ga.), B. Conger, R. Richart and B. Barron. *Obstet Gynecol* 43(6):901-904, 1974.

The relation between herpes simplex type 2 (HSV-2) antibodies and cervical neoplasia was studied in a small group of women (144) who had been part of a cervical cytologic screening campaign in the Barbados, West Indies, since 1964. Serologic specimens were obtained from 50% of the sample, and the serum tested for type-specific herpesvirus antibodies by the complement fixation technique. HSV-2 antibodies were found in 83.3% of the women in this study. Compared with normal women, the relative risk of a woman with HSV-2 antibodies having cervical cancer was 10.4; this relationship is significant. There was no significant relationship between the presence of HSV-2 antibodies and cervical dysplasia. The relationship between HSV-2 antibodies and cervical cancer was not explainable in terms of age, total number of pregnancies, age at first pregnancy, or age at first coitus. A cohort study should be undertaken to determine whether the herpetic infection precedes or follows the development of cervical cancer.

- 2071 EVIDENCE IN FAVOR OF THE EXISTENCE OF HUMAN BREAST CANCER VIRUS. (E.) Moore, D. H. (Inst. Med. Res., Camden, N.J.). *Cancer Res* 34(9):2322-2329, 1974.

Although most human milks destroy or damage the murine mammary tumor virus (MuMTV) and its RNA-directed DNA polymerase (RDDP), RDDP and type B particles are occasionally found in human milk. RDDP is associated with particles having the same buoyant density as MuMTV and with a 35-70S RNA which is characteristic of RNA tumor viruses. Like MuMTV RDDP, and unlike mouse leukemia virus RDDP, human RDDP responds to magnesium ions for activity with a synthetic template, polyribocytidylic-deoxyguanylic. Hybridization studies indicate a relationship between MuMTV RNA and human breast cancer RNA. Using the migration inhibition factor test, positive responses of human leukocytes to homologous *in situ* breast cancer tissue are correlated with responsiveness to MuMTV. Many human sera completely neutralize MuMTV. Some human breast cancer sera contain material that precipitates specifically on the membrane of budding MuMTV virions, and slices of mouse tumors rich in MuMTV react in immunofluorescence tests with sera from some women with breast cancer or fibrocystic mastopathy. Thus, some women harbor a virus of apparent similarity to MuMTV. The means of virus transfer in humans is unknown. RNA

sequences homologous to MuMTV probes are found in human breast cancers, but to date no homologous DNA sequences have been found. The virus does not seem to be endogenous in humans.

- 2072 RNA-DEPENDENT DNA POLYMERASE ASSOCIATED WITH A SIMIAN LYMPHOID CELL LINE DERIVED FROM A HERPESVIRUS SAIMIRI-INDUCED LYMPHOMA. (E.) Yang, S. S. (Natl. Cancer Inst., Bethesda, Md.), D. Ablashi, G. Armstrong and R. C. Ting. *Int J Cancer* 13(1):82-90, 1974.

Simian lymphoid (AA) cells (established from a lymphoma tumor mass taken from an owl monkey inoculated with *Herpesvirus saimiri* (HVS)) were maintained in monolayer culture and treated at the 11th passage with either BrdU or IdU with or without DMSO. Subsequent assays revealed endogenous RNA-dependent DNA polymerase (RDDP) activity associated with a membrane fraction of the AA cell which sediments at a density of 1.15-1.16 g/cm³. The RDDP derived from the AA culture media differed from the DNA-dependent DNA polymerase (DDDP) derived from HSV. The 1.15-1.16 g/cm³ material from the AA culture medium incorporated ³H-ribonucleosides as part of its intrinsic nucleic acid component. The activity of RDDP in the AA culture medium peaked after the 4th day and was either unaffected or inhibited by treatment with BrdU or IdU. These studies were conducted at a time when the host cells were no longer producing *Herpesvirus saimiri*.

- 2073 ANALYSIS OF PARVOVIRUS mRNA BY SEDIMENTATION AND ELECTROPHORESIS IN AQUEOUS AND NONAQUEOUS SOLUTION. (E.) Carter, B. J. (Natl. Inst. Allergy Infect. Dis., Bethesda, Md.). *J Virol* 14(4):834-839, 1974.

- 2074 CHROMATOGRAPHIC ANALYSIS OF ISOACCEPTING tRNAs FROM AVIAN TUMOR VIRUSES. (E.) Taylor, M. W. (Dept. Microbiol., Indiana U., Bloomington), S. Wang, R. Kothari and P. Hung. *J Virol* 14(5):1092-1098, 1974.

- 2075 EFFECT OF CHEMICALLY MODIFIED 70S RNA FROM AVIAN MYELOBLASTOSIS VIRUS (AMV) UPON THE ACTIVITY OF AMV DNA POLYMERASE. (E.) Papas, T. S. (Natl. Cancer Inst., Natl. Inst. Health, Bethesda, Md.), J. Massicot, R. Irwin and M. Chirigos. *J Virol* 14(5):1108-1114, 1974.

- 2076 BIOLOGICAL EXPRESSION OF ANTIGENIC DETERMINANTS OF MURINE LEUKEMIA VIRUS PROTEINS gp69/71 AND p30. (E.) Ikeda, H. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.), T. Pincus, T. Yoshiki, M. Strand, J. T. Agust, E. A. Boyse and R. C. Mellors. *J Virol* 14(5):1274-1280, 1974.

- 2077 STRUCTURE OF THE MOUSE MAMMARY TUMOR VIRUS: CHARACTERIZATION OF BALD PARTICLES. (E.) Cardiff, R. D. (Sch. Med., U. California, Davis), M. Puentes, Y. Teramoto and J. Lund. *J Virol* 14(5):1293-1303, 1974.

- 2078 EFFECT OF β -PROPIOLACTONE INACTIVATION OF POLYOMA VIRUS ON VIRAL FUNCTIONS. (E.) Brown, A. (Dept. Mol. Biol., U. Geneva, Switzerland), R. Consigli, J. Zabielski and R. Weil. *J Virol* 14(4):840-845, 1974.
- 2079 MURINE INTRACISTERNAL A TYPE PARTICLES FAIL TO SEPARATE FROM THE MEMBRANE OF THE ENDOPLASMIC RETICULUM. (E.) Perk, K. (Natl. Cancer Inst., Bethesda, Md.) and J. Dahlberg. *J Virol* 14(5):1304-1306, 1974.
- 2080 ADENOVIRUS ANTIGENS: A MODEL SYSTEM IN MICE FOR SUBUNIT VACCINATION. (E.) Mautner, V. (Natl. Inst. Med. Res., London, England) and H. Willcox. *J Genet Virol* 25(3):325-336, 1974.
- 2081 FURTHER OBSERVATIONS ON THE PRODUCTION OF ONCORNAVIRUSES BY MJY-ALPHA CELL LINE. (E.) Yagi, M. J. (Cancer Res. Lab., U. California, Berkeley). *J Natl Cancer Inst* 53(5):1383-1385, 1974.
- 2082 RNA SYNTHESIS IN HeLa CELLS INFECTED WITH FROG VIRUS 3. (E.) Zylber-Katz, E. (Chanock Ctr. Virol., Hebrew U., Jerusalem, Israel) and P. Weisman. *J Gen Virol* 25(3):405-413, 1974.
- 2083 STRUCTURE AND FUNCTION OF RNA. (Fr.) Burny, A. (Dept. Mol. Biol., U. Brussels, Belgium). *Arch Int Physiol Biochim* 82(4):763-764, 1974.
- 2084 HISTOCOMPATIBILITY GENES (THE H-2 COMPLEX) AND SUSCEPTIBILITY TO MAMMARY TUMOR VIRUS IN MICE. (E.) Muhlbock, O. (Netherlands Cancer Inst., Amsterdam) and A. Dux. *J Natl Cancer Inst* 53(4):993-996, 1974.
- 2085 THE ULTRASTRUCTURAL DEMONSTRATION OF VIRUS-LIKE PARTICLES IN HUMAN LEUKAEMIC CELLS. (E.) Cawley, J. C. (Dept. Med., U. Cambridge, England) and A. Karpas. *Eur J Cancer* 10(9):559-562, 1974.
- 2086 TRACES OF HUMAN RNA TUMOUR VIRUSES IN GUTS, LUNGS AND PHYLOGENETIC TREES. (E.) Anonymous. *New Scientist* 64(923):472, 1974.
- 2087 EXPERIMENTS WITH HUMAN PAPILLOMA VIRUS IN CELL CULTURE. (E.) Cubie, H. A. (Roy. Infirm., Edinburgh, Scotland). *Br J Dermatol* 91(5):569-571, 1974.
- 2088 STRUCTURAL STUDIES OF ADENOVIRUS TYPE-2 HEXON PROTEIN. (E.) Jornvall, H. (Karolinska Inst., Stockholm, Sweden), U. Pettersson and L. Philipson. *Eur J Biochem* 48(1):179-192, 1974.
- 2089 EFFECT OF ACUTE OR CHRONIC INFECTION WITH LACTIC DEHYDROGENASE VIRUS (LDV) ON THE SUSCEPTIBILITY OF MICE TO PLASMACYTOME MOPC-315. (E.) Michaelides, M. C. (Washington U. Sch. Med., St. Louis, Mo.) and S. Schlesinger. *J Immunol* 112(4):1560-1564, 1974.
- 2090 DEMONSTRATION OF TWO IMMUNOLOGICALLY DISTINCT XENOTROPIC TYPE C RNA VIRUSES OF MOUSE CELLS. (E.) Stephenson, J. R. (Natl. Cancer Inst., Bethesda, Md.), S. A. Aaronson, P. Arnstein, R. J. Huebner and S. R. Tronick. *Virology* 61(1):56-63, 1974.
- 2091 PROPERTIES OF MOUSE LEUKEMIA VIRUSES. VII. THE MAJOR VIRAL GLYCOPROTEIN OF FRIEND LEUKEMIA VIRUS. ISOLATION AND PHYSICO-CHEMICAL PROPERTIES. (E.) Moennig, V. (Max Planck Inst. Virus Res., Tübingen, Germany), H. Frank, G. Hunsmann, I. Schneider and W. Schafer. *Virology* 61(1):100-111, 1974.
- 2092 NUCLEOTIDE SEQUENCE ANALYSIS OF THE SV40 -- HIND H DNA FRAGMENT. (E.) Volckaert, G. (Lab. Mol. Biol., U. Ghent, Belgium), A. Van de Voorde and W. Fiers. *Hoppe Seylers Z Physiol Chem* 355(10):1264, 1974.
- 2093 DENSITY CHANGES IN HERPESVIRUS-INFECTED CELLS. (E.) Ross, K. B. (Dept. Microbiol., Emory U. Atlanta, Ga.) and R. J. Ash. *Cytobios* 9(36):227-236, 1974.
- 2094 ONCOGEN INFECTION NUCLEOPROTEID FROM *STATU NASCENDI* STAGES OF CERVICAL CANCER AND HERPES VIRUS HOMINIS. (Ger.) Eschbach, W. (Central Inst. Cancer Res., East German Acad. Sci., Berlin), H. Glathe and B. Nobel. *Arch Geschwulstforsch* 43(4):364-376, 1974.
- 2095 ULTRASTRUCTURAL OBSERVATIONS OF PRIMATE *IN VITRO*: ATTEMPTS TO IDENTIFY ENDOGENOUS C-TYPE VIRUSES. (E.) Helmke, R. J. (Microbiol. Infect. Dis., Southwest Fdn. Res. Education, San Antonio, Tex.), S. S. Kalter, R. L. Heberling and G. C. Smith. *Tex Rep Biol Med* 32(2):610, 1974.
- 2096 C-TYPE PARTICLES IN PLACENTAS OF FOUR MOUSE STRAINS. (E.) Smith, G. C. (Microbiol., Infect. Diseases, Southwest Fdn. Res. Education, San Antonio, Tex.), S. S. Kalter, R. L. Heberling, R. J. Helmke and M. Panigel. *Tex Rep Biol Med* 32(2):617, 1974.
- 2097 STUDIES ON THE TRANSCRIPTION OF ADENOVIRUS TYPE 12. (E.) Ortin, J. (Inst. Genet., U. Cologne, Germany), K. M. Scheidtmann and W. Doerfler. *Hoppe Seylers Z Physiol Chem* 355(10):1235-1236, 1974.

- 2098 HOST GENETIC CONTROL OF RECOVERY FROM FRIEND LEUKEMIA VIRUS-INDUCED SPLE-
NOMEGALY. MAPPING OF A GENE WITHIN THE MAJOR HISTO-
COMPATIBILITY COMPLEX. (E.) Chesebro, B. (Natl.
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Lab., Hamilton, Mont.), K. Wehrly and J. Stimpfling.
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- 2099 MORE PUTATIVE HUMAN TUMOUR VIRUSES. (E.)
weiss, R. A. (No affiliation). *Nature* 252(5480):
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- 2100 A MUTANT VIRUS THAT MAY PEG THE GENES OF
CANCER. (E.) Anonymous *New Scientist*
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- 2101 PERICENTRIOLAR VIRUS-LIKE PARTICLES IN
CHINESE HAMSTER OVARY CELLS. (E.)
Wheatley, D. N. (U. Med. Buildings, Aberdeen,
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- 2102 THE EXPERIMENTAL HIPA PLASMACYTOMA OF
MICE. (Ger.) Pedio, G. (Canton Hosp.,
Zurich, Switzerland). *Pathol Microbiol* 41(2):93-
117, 1974.
- 2103 EXPERIMENTAL HERPESVIRUS HOMINUS TYPE 2
INFECTION IN THE CERVIX OF THE MOUSE. (E.)
Papanikandros, K. (Theagenion Cancer Inst., Thessalo-
niki, Greece), J. Taylor-Papadimitriou and K. Sirma-
kechian. *Cancer Cytol* 13(1), 1973.
- 2104 CELL TRANSFORMATION *IN VITRO* BY HERPES
VIRUS TYPE II. (E.) Skinner, G. R. B.
(Dept. Virol., U. Birmingham, England). *Cancer Cytol*
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- 2105 EFFECTS OF HERPES SIMPLEX VIRUS UPON NORMAL
AND NEOPLASTIC CERVICAL CELLS CULTURES.
CYTOLOGICAL STUDY. (E.) Tortora, M. (Dept. Obstet.,
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- 2106 ULTRASTRUCTURAL EVIDENCE FOR VIRIONS IN
SOLID METASTATIC NODULES OF HUMAN MAMMARY
ADENOCARCINOMA. (E.) Watson, J. H. L. (Henry Ford
Hosp., Detroit, Mich.), J. L. Swedo and R. W. Talley.
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- 2107 THE ROLE OF MACROPHAGES IN CLASSIC MAREK'S
DISEASE. (E.) Campbell, J. C. (Dept. Vet.
Pathol., Bush House, Midlothian, England). *Br J*
Cancer 28(1):79-80, 1973.
- 2108 *IN SITU* HYBRIDIZATION OF VIRAL NUCLEIC
ACIDS IN TUMOUR CELLS. (E.) McDougall,
J. K. (Med. Sch., Birmingham, England), P. H. Galli-
more, A. R. Dunn and K. W. Jones. *Br J Cancer* 28(1):
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- 2109 CHARACTERIZATION OF THE INTERACTION OF
HERPES SIMPLEX TYPE 2 WITH CANCER CELLS
IN A HUMAN CERVICAL CARCINOMA. (E.) Roizman, B.
(Dept. Microbiol., Biophys., U. Chicago, Ill.).
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- See also:
- * (Rev): 1801, 1807, 1814, 1819
 - * (Chem): 1878, 1947
 - * (Immun): 2133, 2150, 2158, 2163, 2172,
2173, 2174, 2175, 2176, 2182,
2183, 2184, 2185, 2186, 2187,
2188, 2189, 2190, 2191, 2192,
2202, 2212
 - * (Epid-Biom): 2266, 2270, 2283

- 2110 IMMUNODIAGNOSIS OF ACUTE LEUKEMIA: DETECTION OF RESIDUAL DISEASE. (E.) Gutterman, J. U. (U. Texas M. D. Anderson Hosp. Tumor Inst., Houston), G. Mavligit, M. A. Burgess, K. B. McCredie, C. Hunter, E. J. Freireich and E. M. Hersh. *J Natl Cancer Inst* 53(2):389-392, 1974.

Bone marrow cells from 25 adult patients with acute leukemia in complete remission were used to stimulate blastogenesis among autologous peripheral blood lymphocytes to detect residual leukemia among the marrow cells. The bone marrows and peripheral blood lymphocytes were taken at intervals of 1-32 months after remission had been induced by chemotherapy. Of 17 patients whose peripheral blood lymphocytes failed to react to autologous remission bone marrow cells, 15 remained in complete remission (median = 10.5 months). In contrast, 5 of 8 patients whose peripheral blood lymphocytes were stimulated by the bone marrow cells subsequently relapsed (median = 6.5 months). The difference in the relapse rate between the two groups was statistically significant. The bone marrow morphology, median percent of bone marrow blasts, and the bone marrow cellularity were similar for both groups of patients. The improved ability to detect residual leukemic disease by the use of bone marrow cells in mixed leukocyte culture with autologous peripheral blood lymphocytes should improve the management of leukemia patients in remission.

- 2111 PHOTOSCAN LOCALIZATION OF GW-39 TUMORS IN HAMSTERS USING RADIOLABELED ANTICARCINO-EMBRYONIC ANTIGEN IMMUNOGLOBULIN G. (E.) Goldenberg, D. M. (U. Kentucky Med. Ctr., Lexington), D. F. Preston, F. J. Primus and H. J. Hansen. *Cancer Res* 34(1):1-9, 1974.

Photoscans and organ radioactivity were assessed in hamsters bearing cheek pouch grafts of a carcinoembryonic antigen (CEA)-producing human colonic carcinoma, GW-39; a human sarcoma, H.S.1; and a hamster amelanotic melanoma, A.Mel.3. The animals were given intracardiac injections of 10-50 $\mu\text{Ci}^{125}\text{I}$ -labeled heterospecific anti-CEA immunoglobulin G (IgG) or normal IgG. The photoscans showed an increased uptake of radioactivity over the tumors and frequently over the areas of the thorax and urinary bladder, regardless of the tumor or the radiolabeled IgG preparation used. Even normal hamsters receiving either radiolabeled preparation showed an increased accretion of radioactivity over the thoracic region. A specific tumor localization, however, was demonstrated in animals bearing small (< 200 mg) GW-39 tumors and given injections of radiolabeled anti-CEA IgG. In fact, even GW-39 tumors of merely 70 mg were visualized in the hamster by administering radiolabeled anti-CEA IgG and scanning 6 to 8 days later. The radioactivity recovered from GW-39 tumors borne in hamsters given injections of radiolabeled anti-CEA IgG revealed an increase of 7.5-20 times that recovered from other tissues. A slightly increased uptake of either the specific or nonspecific radiolabeled preparation was seen in the other, non-CEA-producing tumors studied, which was sufficiently increased over background radiation to permit visualization of the

tumors by photoscanning, especially when the neoplasms were large and vascular. Evidently radio-labeled nonantibody components of heterospecific IgG can be localized in certain tumors and normal tissues by photoscanning. However, tumor localization by anti-CEA-IgG of CEA-producing GW-39 tumors was much more sensitive. Thus, CEA may be a suitable tumor target for radioantibody by photoscanning.

- 2112 DNA POLYMERASES FROM NON STIMULATED AND PHYTOHEMAGGLUTININ STIMULATED NORMAL HUMAN LYMPHOCYTES. (E.) Fridlender, B. (Inst. Biochem. Res., U. Buenos Aires, Argentina), S. Virasoro, S. Blau and J. Mordoh. *Biochem Biophys Res Commun* 60(3):983-990, 1974.

The presence and some properties of DNA polymerases isolated from normal human lymphocytes, nonstimulated and stimulated by phytohemagglutinin, are described. In the nonstimulated lymphocytes two cytoplasmic DNA polymerases were found, one eluting from DEAE cellulose at 0.07 M NaCl (CI_N) and the other at 0.13 M NaCl (CII_N). In the nuclear soluble fraction only one enzyme activity was found (NI_N) which does not adsorb to DEAE cellulose. In the cytoplasm of stimulated lymphocytes only one enzyme activity was detected (CI_S) which elutes from DEAE cellulose at 0.12 M NaCl. The nuclear soluble fraction contained two activities: NI_S , which did not adsorb to DEAE cellulose, and NII_S , which eluted from DEAE cellulose at 0.07 M NaCl. The NI enzymes differed from other DNA polymerases in bovine serum albumin requirement, salt dependence, pH optimum, and ability to incorporate dNTP.

- 2113 ULCERATIVE COLITIS, AUTOIMMUNE EPIPHENOMENA, AND COLONIC CANCER. (E.) Watson, D. W. (Dept. Internal Med., U. California, Davis). *Cancer* 34(3):867-871, 1974.

The risk of developing a carcinoma of the colon is clearly increased in patients with ulcerative colitis. The basis for this relationship, however, is unknown, since the pathogenesis of both the predisposing colitis and the complicating carcinoma remain undefined. Most recent studies have attempted to implicate some type of immune response in the etiology of ulcerative colitis. Humoral antibodies to a colonic epithelial cell antigen have been demonstrated but are of doubtful significance. Perhaps of greater importance is the presence of circulating lymphocytes which are cytotoxic for colonic epithelial cells. These immune phenomena *per se* probably bear no direct relationship to neoplasia since they occur in granulomatous colitis, in which the incidence of carcinoma is far less; cell-mediated immunity (immunologic surveillance) is intact in ulcerative colitis but depressed in granulomatous colitis; and similar immune phenomena are not present in patients with colon cancer without inflammatory bowel disease. It is likely that carcinoma of the colon represents a true complication of ulcerative colitis, relating to the extent of anatomical involvement, duration of the disease, and age of on-

set rather than being an integral part of a more fundamental pathologic process. There is at present no evidence to support a common pathogenetic scheme based on or related to immune mechanisms.

- 2114 FAILURE OF IMMUNOSURVEILLANCE AGAINST CHEMICALLY INDUCED *IN SITU* TUMORS IN MICE. (E.) Andrews, E. J. (Pennsylvania State U. Coll. Med., Hershey). *J Natl Cancer Inst* 52(3): 729-732, 1974.

The ability of a competent host immune system to recognize chemically induced *in situ* tumors in mice was evaluated. Incipient tumors were produced by the administration of 5% 3-methylcholanthrene (MCA) pellets to normal and immunodepressed BALB/c female mice. Two months later, half the animals were subjected to full-thickness autografting of the area containing the MCA pellet. No tumors developed in autografted sites of normal mice. Normal mice with nongrafted sites and both groups of immunodepressed mice had significant tumor development. In a second experiment, spontaneous *in situ* neoplasms were simulated by implantation of weakly antigenic, heavily irradiated, mesenchymal or epidermal tumors into normal and immunodepressed mice. Half the animals had autografting of areas containing the implants. All mice were subsequently challenged with viable tumor fragments. The results indicate that no animal was immunized. Both experiments suggest that in a natural situation where most tumors are small and weakly antigenic, immunosurveillance is ineffective.

- 2115 HEREDITARY IMMUNODEFICIENCY AND LEUKEMOGENESIS IN HRS/J MICE. (E.) Heiniger, H. J. (Jackson Lab., Bar Harbor, Maine), H. Meier, N. Kaliss, M. Cherry, H. W. Chen, and R. D. Stoner. *Cancer Res* 34(1):201-211, 1974.

This study was undertaken to determine whether the difference observed in the incidence of leukemia among the three genotypes of the HRS/J mouse strain (hairless, *hr/hr* and haired, *hr/+* and *+/+*) was related to a general immunodeficiency in the *hr/hr* mutant. Several different experimental approaches yielded the following results. (a) A severe thymic cortical atrophy was observed in *hr/hr* mice beginning at about six months of age, with a concurrent increase in splenic lymphoid elements. (b) Whole-body DNA turnover as well as turnover of DNA, RNA, and protein in thymus, spleen, lymph nodes, and bone marrow were similar in all three genotypes, independent of age and sex. (c) In two *in vivo* test systems, phytohemagglutinin stimulation and plaque assays for sheep RBC hemolysis, the *hr/hr* mutant responded somewhat better than the *+/+* and *hr/+* animals. (d) The ability to produce antibody to tetanus toxoid in the form of aluminum-adsorbed, fluid, and complexed toxoid (in slight antigen excess) was greatly reduced in *hr/hr* mutants. These findings indicate a relative functional defect in the immune system of these mutants. If a deficient "collaboration" among different lymphoid cell types or a deficiency in the proliferative capacity of

immunocompetent cells occurs in mutants, it may result in an ineffective immunosurveillance against leukemogenesis.

- 2116 CARCINOMATOUS NEUROMYOPATHY: 2. IMMUNOLOGICAL STUDIES. AN ELECTROPHYSIOLOGICAL AND IMMUNOLOGICAL STUDY OF PATIENTS WITH CARCINOMA OF THE LUNG. (E.) Paty, D. W. (Newcastle Gen. Hosp., Newcastle upon Tyne, England), M. J. Campbell and D. Hughes. *J Neurol Neurosurg Psychiatry* 37(2): 142-151, 1974.

Macrophage inhibition factor (MIF) was assayed in the presence of a human peripheral nerve extract (PN) to determine the cellular sensitivity to peripheral nerve antigens among 30 patients with lung cancer, 11 patients with lung cancer and neuropathy, 13 patients with chronic nonspecific neuropathy, and 15 normal subjects. The MIF assay results indicated that most of the patients with carcinomatous neuromuscular disease and most of those with chronic nonspecific neuropathy had detectable lymphocyte sensitivity to the PN extract. Nine of the lung cancer patients also had significant cellular sensitivity to the PN antigen; in this group, cellular sensitivity could not be strictly correlated with the presence or absence of subclinical or electrophysiological signs of neuromuscular disease. No sensitivity was found among the normal controls. The data provide no evidence for a primary immunological mechanism in the nonmetastatic carcinomatous neuromuscular syndromes.

- 2117 INHIBITION OF TUMOR-INDUCED LYMPHOCYTE BLASTOGENESIS BY A FACTOR OR FACTORS ASSOCIATED WITH PERIPHERAL LEUKOCYTES. (E.) Hattler, Jr., B. G. (U. Arizona Med. Ctr., Tucson) and B. Soehnlen. *Science* 184(4144):1374-1375, 1974.

A study was made of the effect of elutable factors of leukocytes of 8 different cancer patients on the *in vitro* mixed lymphocyte-tumor cell interaction (MLTI) involving the patients' own lymphocytes and tumor cells. Seven of the patients had squamous cell carcinomas of the lung; 1 had an adenocarcinoma of the stomach. Blastogenic responses of the lymphocytes were based on measurement of incorporation of tritiated thymidine. The mixed cultures were set up with 2×10^5 responding lymphocytes stimulated with 1×10^5 irradiated tumor cells. Lymphocytes eluted by an extensive washing procedure (W5) were stimulated by tumor cells more strongly than were lymphocytes eluted by a single wash (W1). Further, the stimulation of W5 cells by tumor cells was inhibited by the addition of the cell wash eluate to the MLTI culture system, while the stimulation of the W1 cells was unaffected under the same conditions. The active inhibitory component in the cell wash eluate was fractionated into high and low molecular wt fractions which, were inactive separately, but when combined, showed inhibition comparable to that of the unfractionated material. This suggested the possibility that antigen-antibody complexes were responsible for the inhibitory activity. Cell wash eluate from normal leukocytes showed no such inhibi-

tion. The eluates from leukocytes of cancer patients had immunological specificity as revealed by the finding that W5 cells from lung carcinoma patients did not show inhibition when preincubated with the eluate from a patient with adenocarcinoma of the stomach. In addition, the inhibitory material in the cell wash could be absorbed out with the patients W5 cells but not with his tumor cells.

- 2118 ALPHA-FETOPROTEIN AND TERATOMAS OF THE TESTIS. (E.) Shephard, B. G. F. (Roy. Marsden Hosp., London, England). *Proc R Soc Med* 67(4):307-308, 1974.

Serum alpha-fetoprotein (AFP), an embryo-specific alpha-globulin, is found in primary hepatoma, teratomas of all types, viral hepatitis, liver regeneration (not cirrhosis), and secondary liver tumors. Serum levels of 250 times normal are indicative of hepatoma or teratoma, lower levels indicating the possibility of other diseases. Detection is by immunochemical methods using specific anti-alpha-fetoprotein sera. About 45% of teratomas of the testis are positive at diagnostic levels using agar gel precipitation; 75% of the negative cases are positive using immunoradioautography. Screening for AFP is not applicable to or necessary for testicular tumors, although a positive test will be decisive in doubtful cases. There is some indication that the presence of AFP correlates with a poorer prognosis. The test may be useful in the follow up of patients. If the patient has a positive AFP before and after orchidectomy, there must be metastases.

- 2119 THE SIGNIFICANCE OF ALPHA-FETOPROTEIN IN THE SERUM OF PATIENTS WITH MALIGNANT TERATOMAS AND RELATED GONADAL NEOPLASMS. (E.) Ballas, M. (Englewood Hosp., N.J.). *Ann Clin Lab Sci* 4(4):267-275, 1974.

Sera from 11 patients with germ cell gonadal tumors and two patients with clear cell adenocarcinomas of the vagina and ovary were tested for alpha-fetoprotein (AFP) by counterelectrophoresis. The highest AFP levels were found in two cases of yolk sac carcinomas of the endodermal sinus type. Both patients were tested at times of extensive abdominal metastasis and both died within seven months. Of the remaining female teratoma cases, only the serum sample from a woman with an embryonal teratoma with a predominating dysgerminoma was positive. The male germ cells tumors consisted of four pure typical embryonal carcinomas, one embryonal carcinoma with teratomatous and trophoblastic components, and one adult teratoma containing an embryonal carcinoma. Of these cases, two of the typical embryonal carcinomas and the embryonal carcinoma with teratomatous and trophoblastic components were weakly positive for AFP; all had early metastasis and two died within 12 months. Neither case of clear cell adenocarcinoma was positive for AFP. These results indicate that a positive AFP test, particularly in cases with embryonal carcinomas, is indicative of a poor prognosis, being correlated with metastasis and/or

a fatal outcome. The association of endodermal sinus tumors with high serum levels of AFP is compatible with the hypothesis of a vitelline origin.

- 2120 IMMUNOBIOLOGY OF INDUCED TESTIS TUMOR. (E.) Javadpour, N. (Chicago Med. Sch., Ill.). *Urology* 4(1):97-99, 1974.

Genital ridges from 12- 13-day-old mouse embryos were transplanted into the left testes of 50 syngeneic adult mice. Teratocarcinomas which were morphologically identical to testicular teratocarcinomas of the human testes developed in 76% of these testes; the right testes of these animals showed no abnormalities. Retroperitoneal lymph nodes were enlarged and hyperplastic, but showed no evidence of malignant cells. Serum carcinoembryonic antigen (CEA) was within normal limits. In a second experiment, 50 adult mice with genital ridge transplants were injected i.p. with 75×10^6 lymphocytes obtained from the mice in the first experiment. The testes with the genital ridge transplants showed necrotic tumor formation, the histological changes being compatible with rejection. Serum CEA was within normal limits. In the third experiment, 50 adult mice with genital ridge transplants were injected i.p. with lymphocytes obtained from normal adult mice. The findings were essentially the same as in the first experiment. The induced teratocarcinoma appears to possess a tumor-associated antigen which is capable of sensitizing the regional lymphocytes.

- 2121 α_1 -FETOPROTEIN IN PEDIATRIC ONCOLOGY. (It.) Ceci, A. (Inst. Pediatr. Clin., Univ. Bari, Italy), R. Penza and L. Armenio. *Boll Soc Ital Biol Sper* 49(17):972-976, 1973.

Alpert's technique of electrosineresis, which employs rabbit antiserum, was used to determine whether α_1 -fetoprotein (AFP) was present in sera from 34 children with a variety of neoplasms. These patients included 13 with acute leukemia, 6 with Hodgkin's disease, 6 with other forms of lymphoma, 6 with Wilm's tumor, and 3 with neuroblastoma. Only one patient with Hodgkin's disease had a positive test for α_1 -fetoprotein. Originally this patient's serum had been negative, but a positive test was obtained during an intercurrent episode of jaundice which was accompanied by an increase in serum transaminase activities and a positive test for Australian antigen.

- 2122 HEPATOCYTE PROLIFERATION AND α_1 -FETOPROTEIN IN PREGNANT, NEONATAL, AND PARTIALLY HEPATECTOMIZED RATS. (E.) Sell, S. (U. California San Diego Med. Sch., La Jolla), M. Nichols, F. F. Becker and H. L. Leffert. *Cancer Res* 34(4):865-871, 1974.

Serum α_1 -fetoprotein concentrations of pregnant and newborn rats and of rats following partial hepatectomy were measured by radioimmunoassay, and the results correlated to the numbers of hepatocytes synthesizing DNA. Rising concentrations follow rounds

of hepatocellular proliferation indicating that the production of α_1 -fetoprotein is closely coupled to cellular division, i.e., either α_1 -fetoprotein is synthesized transiently and released by a postmitotic cell or it is synthesized prior to mitosis and released after mitosis.

- 2123 RELATIONSHIP OF RAT α_1 -FETOPROTEIN TO GROWTH RATE AND CHROMOSOME COMPOSITION OF MORRIS HEPATOMAS. (E.) Sell, S. (U. California, San Diego, Med. Sch., La Jolla) and H. P. Morris. *Cancer Res* 34(6):1413-1417, 1974.

The serum α_1 -fetoprotein (α_1 F) concentrations of ACI and Buffalo rats bearing 39 different transplantable Morris hepatomas vary from normal (less than 0.06 μ g/ml) to as high as 18,000 μ g/ml. The production of elevated serum α_1 F concentrations by these hepatomas is related to a number of factors including growth rate, degree of differentiation, and chromosome composition. Slowly growing, well-differentiated tumors generally do not produce elevated α_1 F serum concentrations while fast-growing, poorly differentiated tumors produce high serum α_1 F concentrations. However, there are significant exceptions as some fast-growing, near diploid tumors do not produce significant α_1 F serum elevations while some slow-growing, aneuploid tumors may. Therefore, the potential of a given tumor line to produce α_1 F appears to be genetically controlled but the degree of expression of this potential is dependent upon the growth rate of the tumor.

- 2124 RAT ALPHA₁ FETOPROTEIN: APPEARANCE AFTER GALACTOSAMINE-INDUCED LIVER INJURY. (E.) Sell, S. (U. California, San Diego, Med. Sch., La Jolla) R. D. Reynolds and W. Reutter. *J Natl Cancer Inst* 53(1):289-291, 1974.

Twelve male Charles River CD rats received two i.p. injections (nine hr apart) of galactosamine (Gal N)-HCl (375 mg/kg) dissolved in NaCl. Blood was obtained by cardiac puncture from one group of rats on days 0, 2, 6, 8, 10, and 11 and from another group on days 1, 3, 5, 7, 9, and 11. The serum samples were analyzed for alpha₁-fetoprotein (α_1 F) by radioimmunoassay. The serum α_1 F concentrations rose sharply between 48 and 72 hr after Gal N administration, remained elevated for 3-9 days, then fell sharply back to within the normal range. These elevations were temporally associated with the proliferation of hepatocytes which occurred as a restitution response to the liver injury induced by Gal N.

- 2125 AN ISOENZYME OF 5'-NUCLEOTIDE PHOSPHODIESTERASE AND α -FETOPROTEIN IN HUMAN HEPATIC CANCER PATIENT SERA. (E.) Tsou, K. C. (Sch. Med., U. Pennsylvania, Philadelphia), M. G. McCoy and K. W. Lo. *Cancer Res* 34(10):2459-2463, 1974.

A new histochemical method for the detection of the Band V isoenzyme of 5'-nucleotide phosphodiesterase

and the relationship between this isoenzyme and α -fetoprotein were investigated. The isoenzyme was detected in sera from 38 of 43 primary hepatomas (88%), while α -fetoprotein was detected by immunodiffusion in only six of the same sera. Of the 37 α -fetoprotein-negative samples, 18 were retested for α -fetoprotein by counterimmunoelectrophoresis. Of this group, six were found to be positive. For liver involvement with primary cancer of other organs, 44 of 55 sera (80%) showed the Band V isoenzyme. Immunoelectrophoresis of normal, cord, and hepatoma (both α -fetoprotein-positive and -negative) sera and ascites fluid showed the 5'-nucleotide phosphodiesterase isoenzyme and α -fetoprotein to be of different electrophoretic mobilities. The 5'-nucleotide phosphodiesterase Band V isoenzyme and α -fetoprotein were therefore demonstrated to be independent markers for hepatoma.

- 2126 RADIOIMMUNOASSAY OF ALPHA-FETOPROTEIN. V. INFLUENCE OF AGE ON THE PHYSIOLOGICAL SERUM ALPHA-FETOPROTEIN LEVEL IN MAN AND IN RAT. (E.) Masseyeff, R. (Fac. Med., Nice, France), J. Gilli, B. Krebs, C. Bonet and H. Zrihen. *Biomedicine* 21(8):353-357, 1974.

The radioimmunoassay (RIA) double-antibody technique was used to measure the α -fetoprotein (AFP) levels in serum samples from 200 children aged 3 wk to 15 yr, 192 adults aged 20-60 yr, and 16 adults aged 70-98 yr; all subjects were clinically healthy. There was a steep decrease in AFP during the first yr. With few exceptions, the level reached the low basal range by the end of the second yr and was maintained without significant change until about 60 yrs of age. Thereafter, there was a small but significant decrease in the AFP level. During the first postnatal yr, the AFP levels were highly variable, ranging from more than 10,000 to 6 ng/ml; this was not related to premature birth. The AFP levels did not appear to vary with sex. In the Sprague-Dawley rat, the general pattern of decrease in AFP concentration was similar to that observed in man except that at every stage the concentrations were higher in the rat. Also, levels in the pubertal rat were 7 times higher than in the adult rat while in man the basal levels were reached long before puberty. The persistence of relatively stable levels throughout postnatal life in both rat and man suggests that the rate of synthesis and catabolism of AFP is regulated by physiological factors analogous to those which maintain the normal concentration of other protein constituents in the blood.

- 2127 CORRELATION BETWEEN CLINICO-PATHOLOGICAL FEATURES OF MALIGNANT TUMORS AND CELL SURFACE IMMUNOGLOBULINS. (E.) Izsak, F. C. (Donolo Gov. Hosp., Jaffa, Israel), H. J. Brenner, E. Landes, M. Ran and I. P. Witz. *Isr J. Med Sci* 10(6):642-646, 1974.

A prospective study was made on 25 patients with malignant disease, in an attempt to correlate the clinical course and histological features with the

presence of cell surface immunoglobulins. The criteria evaluated were clinical staging, tumor growth rate, factors related to morbidity and adaptability of the host and the histopathological grade. All factors were scored numerically and the tumors divided into groups of high or low malignant potential. The immunoglobulin cell coat was evaluated by two methods: elution and radioimmunoassay. A close correlation between the histopathological and clinical criteria was demonstrated. Moreover, the presence of immunoglobulins on the cell membrane demonstrated an apparent association with the estimated high malignant potential. Of the 12 tumors with a high malignancy index, 9 had IgG coating compared with 5 of 13 tumors with a low malignancy index. This finding supports the view that a blocking factor, interfering with immunologically mediated tumor cell destruction, may exist.

- 2128 SOME ASPECTS OF HUMORAL IMMUNITY IN GERM-FREE AND CONVENTIONAL SJL/J MICE IN RELATION TO AGE AND PATHOLOGY. (E.) Seibert, K. (Creighton U. Sch. Med., Omaha, Neb.), M. Pollard and A. Nordin. *Cancer Res* 34(7):1707-1719, 1974.

The humoral immune competence of 130 germ-free and 137 conventional SJL/J mice in relation to age was evaluated by means of the hemolytic plaque assay. Spleen cells from 2- to 14-month-old animals were tested for the presence of specific IgM and γ_1 antibody-forming cells on days 4, 5, and 6 after i.p. immunization with sheep RBC. The results show a similar plaque response between germ-free and conventional animals at all levels, as reflected in their ability to form specific antibody against sheep erythrocytes. The peak response for both IgM and γ_1 production occurred at age 4 months with a subsequent progressive, marked, age-related decline. The γ_1 response was more severely impaired with age than the IgM response. Animals with the lowest plaque-forming cell responses had high spleen weights and the most severe histological lesions of any of the groups studied. Animals with lymphoreticular lesions characterized by a predominance of reticulum cells, by a depletion of small lymphocytes and plasma cells, and by the presence of significant areas of fibrosis and cellular depletion had low or negative plaque-forming cell responses and low levels of γ -globulin. Animals with plasmacytic or lymphocytic hyperplasia had consistently high globulin levels but an unpredictable plaque-forming cell response. The peripheral blood total leukocyte and lymphocyte counts decreased significantly with age and progress of the disease.

- 2129 SURFACE IMMUNOGLOBULINS IN CHRONIC LYMPHATIC LEUKAEMIA, MACROGLOBULINAEMIA AND MYELOMATOSIS. (E.) Knapp, W. (Inst. Exp. Gerontol., Organ. Health Res., TNO, Rijswijk, Netherlands), H. R. E. Schuit, R. L. H. Bolhuis and W. Hijmans. *Clin Exp Immunol* 16(4):541-552, 1974.

Lymphocytes were obtained from the bone marrow and peripheral blood of patients with chronic lymphatic leukemia (CLL), multiple myeloma (MM), and the mac-

roglobulinemia of Waldenstrom (MW). Direct immunofluorescence techniques were used to detect surface immunoglobulins (Ig) on these cells. In CLL, a monoclonal proliferation of cells with surface Ig was found, but the percentage of cells with cytoplasmic fluorescence was normal. In MW, the percentage of lymphocytes bearing surface IgM was remarkably high, sometimes reaching 100%. However, there were also MW cases with decreased numbers of IgM membrane-positive cells. The cases with a high percentage of peripheral lymphocytes with membrane-bound IgM tended to show a high percentage of cells with cytoplasmic IgM in the bone marrow. The percentage of peripheral lymphocytes with membrane-bound Ig in patients with MM was decreased or within normal limits; there was no increase in IgG and probably not in IgA-carrying cells. The data suggest that MM can be considered as a neoplasia of already differentiated Ig-secreting cells, localized in the bone marrow. They support the central role of human bone marrow in antibody production.

- 2130 CHRONIC LYMPHATIC LEUKEMIA AND HUMORAL IMMUNITY. (Ger.) Paulisch, R. (Westend Clin., Free U., Berlin, Germany). *Verhandl Dtsch Ges Inn Med* 79:510-511, 1973.

Electrophoretic analyses of immunoglobulins were performed on 160 male and 113 female patients with chronic lymphatic leukemia. Normal γ -globulin levels were found in over 50% of the patients. A tendency towards decreased γ -globulin levels was found in 23 patients, and hyper- γ -globulinemia was detected in 27 cases. Pronounced hypo- γ -globulinemia was found in 62 patients during the first examination. Seventeen of these patients then showed increasing γ -globulin levels in association with marked symptomatic improvement. Paper-electrophoretic analysis of 75 patients with chronic lymphatic leukemia revealed normal γ -globulin levels in 66 cases while immunoelectrophoretic analyses demonstrated antibody deficiency in all but 37 patients. The findings indicate that reduction of immunoglobulin levels is fairly common in chronic lymphatic leukemia and cannot always be detected by paper electrophoresis.

- 2131 THE SYNTHESIS AND ASSEMBLY OF IMMUNOGLOBULINS BY MALIGNANT HUMAN PLASMACYTES. III. HETEROGENEITY IN IgA POLYMER ASSEMBLY. (E.) Buxbaum, J. N. (Manhattan VA Hosp., N.Y.), S. Zolla, M. D. Scharrf and E. C. Franklin. *Eur J Immunol* 4(5):367-369, 1974.

The pathways of immunoglobulin synthesis and assembly were studied in bone marrow cells from nine multiple myeloma patients whose sera contained substantial amounts of homogeneous IgA1 myeloma proteins. Six of eight cell samples contained molecules which had molecular weights consistent with free light chains and were precipitable with antisera directed toward immunoglobulin light chain antigenic determinants. The molecules were present in excess of those required to form the complete α_2L_2 molecules. Cell samples from two patients contained little or no free light chains. After 1 hr of incubation, the

major α -chain-containing intracellular molecule in eight samples was the α_2L_2 monomer. This molecule was precipitable with anti-light chain antiserum and could be totally reduced to α - and light chains. Its electrophoretic mobility corresponded to that of the murine γ_2L_2 marker. In five of seven secretions, 20-50% of the IgA existed as polymers larger than α_2L_2 . In the other two, only small amounts of polymers were found extracellularly. The cytoplasm of one patient contained such polymers intracellularly. Human myeloma cells synthesizing IgA proteins appear to be very similar to human and murine myeloma cells synthesizing other classes of immunoglobulins.

2132 LYMPHOCYTE REACTIVITY TO AUTOCHTHONOUS TUMOR CELLS IN DOGS WITH SPONTANEOUS MALIGNANCIES. (E.) Tsoi, M. S. (U. Washington Sch. Med., Seattle), P. L. Weiden and R. Storb. *Cell Immunol* 13(3):431-439, 1974.

Lymphocyte reactivity to autochthonous tumor cells was determined by using fresh, incubated, cryopreserved, or trypsinized tumor cells from 29 dogs with malignant lymphoma and 24 dogs with solid tumors. Lymphocytes were stimulated *in vitro* by autochthonous irradiated tumor cells and, after six days in culture, incubated with 3H -thymidine. The ratio of cpm of stimulated over nonstimulated cultures was determined. In 18 of 29 lymphoma dogs and 15 of 24 solid tumor dogs, significant reactivity of lymphocytes to autochthonous tumor cells was seen. No consistent effect of autologous serum on lymphocyte reactivity was found. It is concluded that tumor cells from most dogs with spontaneous malignancies have tumor-associated antigens capable of stimulating autochthonous lymphocytes in culture.

2133 MURINE LEUKEMIA VIRUS GROUP-SPECIFIC ANTIGEN EXPRESSION IN AKR MICE. (E.) Hilgers, J. (Stanford U. Sch. Med., Calif.), A. Decleve, J. Galesloot and H. S. Kaplan. *Cancer Res* 34(10):2553-2561, 1974.

The distribution of the group-specific murine leukemia virus (MuLV) antigen was studied by immunofluorescence and immunofluorescent absorption in normal embryonic, neonatal, and postnatal AKR mice and in leukemic mice of this strain. MuLV-gs antigens were first detected during the first postnatal wk in the liver, spleen, bone marrow, and serum, and during the second postnatal wk in the thymus and the kidney. A variety of other tissues, notably the placenta, uterus, ovaries, and bones, were also positive. Ten- to 18-day-old embryos were consistently negative. MuLV-gs antigen appeared in normal liver two-three days after birth, reached peak levels between days 5-12, then gradually disappeared and remained absent during normal adult life. In mice with disseminated leukemia, infiltrating tumor cells caused another peak of gs antigen expression in the liver. Hematopoietic cells rather than hepatocytes seem to be the productively infected cells in the neonatal liver. Spleen, bone marrow, and lymph nodes were highly positive throughout adult life and showed little further increases in antigen levels during leukemogenesis. Antigen levels

were relatively low in the thymus of normal adult AKR mice but very high in leukemic animals. The blood serum and kidney showed a broad peak of antigen expression at approximately 10-30 days of age; in normal mice, this was followed by a decline, possibly due to an immune response to MuLV antigens. Leukemic adults developed a very high level of antigen in the serum and kidneys. The propagation of MuLV in the tissue(s) of origin and its rapid spread to many other tissues soon after birth presumably account in part for the high susceptibility of the AKR strain to the development of leukemia.

2134 SERUM α_2 -GLOBULINS IN BREAST CARCINOMA. (E.) Minton, J. P. (Ohio State U., Coll. Med., Columbus) and M. A. Bianco. *Arch Surg* 109(2): 238-240, 1974.

The serum proteins of 48 patients with adenocarcinoma of the breast were studied by electrophoresis, with particular attention to the α_2 -globulin fraction, and compared with sera of 162 apparently healthy persons. The α_2 -globulin fraction was elevated in 33 of 50 patients (in one of 11 with local disease and in 32 of 39 with spread beyond local nodes). The serum albumin level was depressed in 32 of 50 patients (two of 11 with local disease and 30 of 39 with spread). The α_2 -globulin elevations correlated well with bone metastases. Elevated α_2 -globulin levels may represent a response by an individual's immunoregulatory mechanism to the foreign antigen present in the metastatic tumor. It is suggested that α_2 -globulin levels are valuable indicators of distant metastases in breast cancer.

2135 IMMUNOLOGICALLY INDUCED INHIBITION AND ENHANCEMENT OF TUMOR GROWTH (EHRlich ASCITES TUMOR): SIGNIFICANCE OF DIFFERENT ANTIGENIC PREPARATIONS. (Ger.) Schweizer, K. (Dept. Med. Microbiol., Technical Coll., Aachen, Germany), G. Gillissen and W. Lutzeyer. *Med Microbiol Immunol (Berl)* 159(3): 251-260, 1974.

Immunologically induced inhibition and stimulation of solid Ehrlich ascites tumor (EAT) was studied in male NMRI mice. The growth of solid EAT was inhibited when the animals were immunized by four s.c. injections of the soluble moiety of EAT material, but stimulation of the tumor growth occurred when the insoluble fraction of EAT material was used for immunization. Immunizing animals in the same way with antigenic material from normal connective tissue produced a similar, but less pronounced effect. A single i.v. injection of soluble EAT material, obtained by freezing and thawing, and injected a few days before tumor transplantation, facilitated tumor development, while soluble material obtained by ultrasonic treatment had no effect. Insoluble EAT material obtained by ultrasonic treatment facilitated tumor growth when injected i.v. three days before tumor transplantation. This effect was abolished by heating the material for 30 min at 56 C. Essentially the same results were obtained with insoluble material from spleen tissue. Insoluble EAT material injected i.v. 19 days before tumor transplantation

inhibited tumor growth; this effect was not abolished by heating of the material. While insoluble material from spleen tissue also inhibited the tumor growth, no inhibition occurred when heated insoluble material was used. The lack of effect of the extract obtained by ultrasonic treatment is probably due to the difficulty involved in extracting soluble antigens by this technique. These findings indicate that the use of insoluble EAT material left after disintegration of cells by ultrasound and heat is the most suitable procedure for studying tumor-specific antigen.

2136 COMPARATIVE IMMUNOELECTROPHORETIC STUDY OF EXTRACTS FROM LS FIBROBLASTS AND FROM THE TUMORS THEY PRODUCE WHEN INJECTED INTO MICE. (It.) Benassi, G. (Inst. Gen. Pathol., U. Ferrara, Italy), G. Berti and P. Melandri. *Tumori* 60(3):211-220, 1974.

Immunoelectrophoresis of aqueous extracts of LS fibroblasts and of sarcomas induced by s.c. injection of LS cells into newborn C3H mice (Tu/LS) against rabbit anti-LS sera and rabbit anti-Tu/LS sera produced a number of precipitation lines, indicating the presence of antigens. These two extracts gave similar patterns on immunoelectrophoresis, but antigens were probably present in different quantities. However, in anti-LS sera adsorbed on tumor extracts an antibody was present capable of reacting with an antigen in the LS extract. This antigen, which did not appear to be present in Tu/LS tumor cells, might indicate that a more incompatible cell clone had been eliminated from the population of growing tumor cells. Alternatively, an antigen which is synthesized by LS fibroblasts *in vitro* might not be produced by the animal *in vivo*.

2137 ROSETTE FORMATION IN NORMAL SUBJECTS AND PATIENTS WITH CHRONIC LYMPHATIC LEUKEMIA. (Ger.) Fink, U. (1st Med. Clin., Technical U., Munich, Germany), J. Strebel, J. Weig, F. Sepp, J. Rastetter and N. Muller-Berat. *Verh Dtsch Ges Inn Med* 79:543-545, 1973.

Using nonsensitized sheep lymphocytes, rosette formation was compared in lymphocytes from 29 normal subjects and 25 patients with chronic lymphatic leukemia. Immediate rosette formation in healthy blood donors averaged $30.1 \pm 3.6\%$ (9-55%) at room temperature and $54.7 \pm 2.8\%$ (40-73%) after overnight storage at 4 C. A significant reduction in the rosette count to 7.3% was observed in patients with chronic lymphatic leukemia. The rosette count increased to 13.4% following cold incubation. An inverse relationship was found between the percentage of rosette-forming lymphocytes and the blood lymphocyte count. Regarding the absolute values of lymphocytes and rosette counts, the rosette-forming lymphocyte count was normal or, in some cases, slightly increased in patients with chronic lymphatic leukemia. Because of the elevated blood lymphocyte count, the percentage of rosettes was decreased in 12 untreated patients. Treatment of ten patients with spleen irradiation, extracorporeal blood irradiation, cytostatics, ACTH, and steroids reduced the lymphocyte counts, increased rosette

formation, and led to clinical improvement. Rosette counts were almost normal in three patients who obtained complete remissions. Although these patients have a normal T-cell population, this is diluted by B-cells and/or leukemic lymphocytes.

2138 CROSS-REACTING TUMOR-ASSOCIATED ANTIGEN(S) OF ADENOVIRUS TYPE 9-INDUCED FIBROADENOMAS AND A CHEMICALLY INDUCED MAMMARY CARCINOMA IN RATS. (E.) Ankerst, J. (Dept. Med. Microbiol., U. Lund, Sweden), G. Steele, Jr. and H. O. Sjogren. *Cancer Res* 34(8):1794-1800, 1974.

Lymphocytes from five female W/Fu rats bearing mammary fibroadenomas were found to share a common reactivity against fibroadenoma target cells, as demonstrated by lymphocyte cytotoxicity tests on ^{125}I -iododeoxyuridine target cells and by microcytotoxicity tests. These lymphocytes were also cytotoxic to target cells derived from a rat mammary carcinoma induced by 3,2'-dimethyl-4-aminobiphenyl. Inversely, lymphocytes from a female W/Fu rat bearing this 3,2'-dimethyl-4-aminobiphenyl-induced mammary carcinoma were cytotoxic to the carcinoma and the fibroadenoma target cells. Neither the immune lymphocytes from fibroadenoma-bearing rats nor those from the rats with the mammary carcinoma were cytotoxic to polyoma virus-induced sarcoma cells or to normal rat breast cells. Sera from each of the the fibroadenoma-bearing rats inhibited the cytotoxic effect of lymphocytes from rats bearing fibroadenoma or carcinoma against both mammary fibroadenoma and carcinoma target cells. Sera from the rat with the 3,2'-dimethyl-4-aminobiphenyl-induced mammary carcinoma inhibited the activity of its own lymphocytes on either fibroadenoma or carcinoma target cells. These results indicate a common tumor-associated antigenicity among the mammary fibroadenomas and a shared (tissue type-specific?) antigen between the mammary fibroadenomas and the chemically induced mammary carcinoma.

2139 MORPHOLOGIC AND FUNCTIONAL STUDIES IN LYMPH NODES REGIONAL TO CANCER. (E.) Tsakraklides, V. (Sloan-Kettering Inst., New York, N.Y.), E. Tsakraklides and R. A. Good. *Clin Bull* 4(1):20-24, 1974.

Regional lymph nodes in uterine, breast, and colorectal cancer can be morphologically classified into four groups designated: lymphocyte predominance, germinal center predominance, lymphocyte depletion, and unstimulated. The survival rate is generally high among patients with lymphocyte predominance, low in patients with lymphocyte depletion, and intermediate in patients with germinal center predominance and unstimulated patterns. It is postulated that lymph nodes with lymphocyte predominance may be actively engaged in a cell-mediated immune response, whereas nodes with germinal center predominance may be responding with the production of humoral antibodies. This hypothesis is supported by the results of *in vitro* studies which show that lymph nodes with lymphocyte predominance contain the highest proportion of T cells and show a high stimulation with phytohemagglutinin (PHA), a T cell mitogen. Nodes with germinal center predominance contain relatively

high proportion of B cells and show a low stimulation index with PHA. The lymphocyte depletion pattern shows an overall reduction that appears to affect the T cell population more than the B, and may be related to exhaustion or inhibition of the immune system. The unstimulated pattern may result from non-antigenic or weakly antigenic tumors; this pattern appears to be heterogeneous both morphologically and functionally. The high survival rate in patients with lymphocyte predominance may be associated with the T cell function, while the lower mean survival rate in patients with germinal center predominance may be associated with the production of blocking factors.

2140 PERIPHERAL BLOOD 'ROSETTE FORMING LYMPHOCYTES' IN DOWN'S SYNDROME. (E.)

Burgio, G. R. (Pediatr. Clin., Pavia, Italy), A. G. Ugazio and L. Nespoli. *Experientia* 30(7):818, 1974.

Peripheral blood lymphocytes were obtained from 25 patients with Down's syndrome (trisomy of the G group) and from 25 mentally retarded, karyotypically normal subjects from the same institution. The age range was 18-30 yr for both groups. The lymphocytes from the Down's syndrome patients showed a marked impairment in the maximum response to phytohemagglutinin (PHA). The percentage of circulating T-lymphocytes in these patients was also significantly lower than in the control group. Recent studies in children with Down's syndrome failed to show any impairment in PHA-responsiveness. Thus, thymus-dependent function appears to decline much more rapidly in Down's syndrome patients than in the general population.

2141 ULTRASTRUCTURAL, IMMUNOLOGIC, AND FUNCTIONAL STUDIES ON SÉZARY CELLS: A NEOPLASTIC VARIANT OF THYMUS-DERIVED (T) LYMPHOCYTES. (E.)

Zucker-Franklin, D. (New York U. Med. Ctr., N.Y.), J. W. Melton III and F. Quagliata. *Proc Natl Acad Sci USA* 71(5):1877-1881, 1974.

The vast majority of human lymphoid neoplasms examined to date have been associated with a proliferation of bone marrow-dependent (B) lymphocytes. In an effort to delineate human tumors of T-cell (thymus dependent) lineage, use was made of the peripheral blood leukocytes of 16 subjects with various forms of mycosis fungoides. The abnormal cells in the circulating blood of these patients were morphologically identical to those that infiltrated their nodes and skin. Electron microscopic examination revealed that these neoplastic lymphocytes (Sézary cells) had "cerebriform" nuclei and an abundance of cytoplasmic fibrils not described heretofore. The Sézary cells were nonadherent and nonphagocytic and usually responded to stimulation with phytohemagglutinin, refuting earlier suggestions that the cells represent monocytes or histiocytes. In contrast to chronic lymphocytic leukemia lymphocytes, the Sézary cells lacked surface immunoglobulin and receptors for complement. Ultrastructural analysis identified Sézary cells in the center of

directly formed rosettes (E-rosettes) characterizing the behavior of T lymphocytes in this test. Although some Sézary cells lacked both T and B cell-surface properties, these observations generally support the view that the Sézary cell is a neoplastic variant of a thymus-derived lymphocyte.

2142 ACTIVATION OF THE PERIPHERAL LYMPHOCYTES IN THE COURSE OF THE IMMUNE RESPONSE TO

TRANSPLANTED SV40-TRANSFORMED TUMOUR CELLS IN HAMSTERS. (E.) Nekvasil, M. (Inst. Sera, Vaccines, Prague, Czechoslovakia) and J. Pekárek. *Immunology* 27(1):159-162, 1974.

Estimation of the activation of peripheral lymphocytes by nucleolar staining patterns was used to evaluate the immune response of Syrian hamsters injected s.c. with simian virus 40 (SV40)-transformed hamster cells. The average percentage of activated lymphocytes was 9.5% in control animals and 20.6-30.8% in tumor bearing animals 7-15 days after inoculation; this difference was significant. After 3 wk, when the tumors were macroscopically visible, the percentage of activated lymphocytes fell below control levels. Animals which rejected the transplanted tumor cells and did not develop macroscopically observable tumors continued to show significantly elevated levels of activated lymphocytes.

2143 BURKITT'S LYMPHOMA: A B OR T CELL TUMOUR?

(E.) Magrath, I. T. (Uganda Cancer Inst., Kampala). *Eur J Cancer* 10(2):83-88, 1974.

Nine of 25 tumors (36%) confirmed both histologically and cytologically as Burkitt's lymphoma responded to *in vitro* phytohemagglutinin stimulation by increased DNA synthesis (measured as tritiated thymidine uptake), and all of six different tumors tested were able to form some spontaneous rosettes with washed sheep erythrocytes (both T-cell characteristics), as well as with antibody and complement treated sheep erythrocytes (a B-cell characteristic). These findings do not appear to be related to lymphocyte contamination of the tumor cells. Several possible explanations for these findings are offered; 1) each tumor may contain both cell types by virtue of a polyclonal origin; 2) some cells are capable of simultaneously expressing both T and B properties; and 3) differentiation from one cell type to the other is occurring within the tumor cell population.

2144 LYMPHOCYTE TRANSFORMATION AND IMMUNOGLOBULINS IN CHILDREN WITH ACUTE LYMPHATIC

LEUKEMIA AND MALIGNANT TUMORS. (Ger.) Pappas, A. (Clin. Internal Med. I, U. Saarland, Homburg/Saar, Germany), W. Wahlen, O. Kausch, P. G. Scheurlen and J. B. Mayer. *Verhandl Dtsch Ges Inn Med* 79:429-432, 1973.

In vitro lymphocyte transformation was measured quantitatively in peripheral blood from ten children with acute lymphatic leukemia and five children with malignant tumors (Wilms tumors, neuroblastoma,

and Hodgkin's disease). The transformation rate was determined from ^{14}C -thymidine incorporation in the presence of phytohemagglutinin and tuberculin. The patients were treated with vincristine, methotrexate, prednisolone, cyclophosphamide, and actinomycin D. Cytostatic agents considerably reduced blood lymphocyte transformation in the presence of tuberculin and phytohemagglutinin in children with acute lymphatic leukemia. Normalization of the ^{14}C -thymidine incorporation during suppurating infections was observed in all but two cases. This normalization may be due to a stimulation of the cellular immune system, resulting in the production of a functionally intact lymphocyte population in the peripheral blood. The rate of lymphocyte transformation was consistently below normal in patients with malignant tumors in whom transformation did not normalize during infections.

- 2145 SURFACE IMMUNOGLOBULINS AND LYMPHOCYTE-SPECIFIC SURFACE ANTIGENS ON LEUKAEMIC RETICULOENDOTHELIOSIS CELLS. (E.) Stein, H. (Inst. Pathol., U. Kiel, W. Germany) and E. Kaiserling. *Clin Exp Immunol* 18(1):63-71, 1974.

Hairy cells from two cases of leukemic reticuloendotheliosis were studied for their enzyme content, adherence to nylon wool columns, phagocytosis, and the presence of surface immunoglobulins and lymphocyte-specific surface antigens. The cells reacted negatively for peroxidase, chloroacetate-esterase, alpha-naphthylacetate-esterase and naphthol-AS-acetate-esterase. They did not adhere to nylon wool columns nor did they show significant phagocytosis. Most of the hairy cells were found to be positively labeled for surface immunoglobulins of different classes; μ chain-positive hairy cells were predominant in number. The data suggest that hairy cells are closely related to lymphatic cells of the B-cell type. They exclude with some certainty the possibility that hairy cells are directly derived from cells of the myeloid system, particularly monocytes, or from classical reticulum cells of the lymphatic tissue.

- 2146 PRODUCTION OF COLONY-STIMULATING FACTOR BY MALIGNANT LEUKOCYTES. (E.) Golde, D. W. (Cancer Res. Inst., U. California, San Francisco), B. Rothman and M. J. Cline. *Blood* 43(5):749-756, 1974.

Considerable evidence suggests that colony-stimulating factor (CSF) is a humoral regulator of leukopoiesis. The levels of CSF in the serum and urine of leukemia patients and the *in vitro* responsiveness of leukemia cells to CSF indicate that leukemia may be a primary disorder of leukopoietic regulation. The production of CSF by leukemic cells was studied. Conditioned medium from cultured leukemic cells was tested for colony-stimulating activity against normal human bone marrow using a two-layer agar colony assay technique. Cells from patients with acute myelogenous leukemia and a patient with chronic myelogenous leukemia in blast crisis did not elaborate CSF, nor did acute lymphocytic leukemia cells. CSF production was observed

with cells obtained from patients with chronic myelogenous leukemia in the chronic phase and two patients with acute myelomonocytic leukemia. In acute leukemia, the cellular production of CSF correlated closely with morphologic and functional maturation along the monocyte-macrophage line. Adherent cells within the leukemic population appeared to be primarily responsible for CSF production. Thus, neoplastic hematopoietic cells may produce CSF in relation to their capacity for mononuclear leukocyte differentiation.

- 2147 CYTOCHEMICAL AND ULTRASTRUCTURAL STUDIES CONCERNING THE CELL COAT GLYCOPROTEINS IN NORMAL AND TRANSFORMED HUMAN BLOOD LYMPHOCYTES. I. VARIATIONS OF SIALIC ACID CONTAINING GLYCOPROTEINS SUBSEQUENT TO TRANSFORMATION OF T AND B LYMPHOCYTES BY VARIOUS KINDS OF STIMULATING AGENTS. (E.) Anteunis, A. (St. Antoine Hosp., Paris, France). *Exp Cell Res* 84(1/2):31-39, 1974.

Hydrochloric-phosphotungstic acid (PTA) staining and the Rambourg technique were used to study the amount and topographical distribution of sialic end groups carried by the cell coat glycoproteins of human blood T and B lymphocytes after blast transformation. The transformation was immediately followed by a transient decrease in the surface labeling in both T- and B-derived lymph cell lines, irrespective of the nature of the stimulating agent used for the induction of transformation (phytomitogens, antilymphocyte sera, tuberculin, and anti-F(ab') sera). Upon reaching their final cyto-differentiation step, the cells of both lines seemed to recover their initial PTA staining patterns, as observed in the controls. This transient decrease in the relative number of sialic acid end groups during a period of dramatically rapid cell growth and multiplication can be interpreted as reflecting an 'incomplete maturation' of the newly synthesized cell coat glycoproteins.

- 2148 SIMILARITIES OF Fc RECEPTORS IN HUMAN MALIGNANT TISSUE AND NORMAL LYMPHOID TISSUE. (E.) Tonder, O. (U. Kansas Med. Ctr., Kansas City), P. A. Morse, Jr. and L. J. Humphrey. *J Immunol* 113(4):1162-1169, 1974.

The Fc receptor activity in various tissues was studied using hemadsorption to cryostat sections of fresh frozen tissue or rosette formation with single cells in suspension. Indicator cells (EA) were sheep RBC sensitized with various amounts of rabbit IgG antibodies (A). Malignant tissues and cells showed very similar behavior to lymphoid tissue and peripheral blood lymphocytes and monocytes, although adsorption of noncomplexed A to monocytic areas of spleen was quantitatively stronger than to B lymphocytic areas and malignant tissues. Receptor activity varied with the degree of sensitization of EA with lymphocytes. This indicates that Fc receptor is not a property of distinct subpopulations of the reactive cell types. Apparently, the presence and availability of this receptor fluctuate in or on each cell. Treatment of tissue sections or single cells with

neuraminidase in various concentrations showed a similar enhancing effect on malignant cells, lymphocytes, and monocytes. The results suggest that the Fc receptors possessed by the three cell types are similar in nature and properties.

2149 SURFACE T- AND B-CELL MARKERS ON MURINE LYMPHOMAS AND PLASMACYTOMAS. (E.)

Ramasamy, R. (Dept. Pathol., U. Cambridge, England) and A. J. Munro. *Immunology* 26(3):563-570, 1974.

Seven murine lymphomas and three plasmacytomas were examined for the distribution of the theta antigen, immunoglobulin determinants, the receptor for Fc portion of antigen-antibody complexes, and the receptor for the third component of complement (C3). The theta-bearing tumor lacked C3 and Fc receptors and easily detectable surface immunoglobulin. The theta-negative lymphomas, while being morphologically lymphocytic, lacked all but the Fc receptors. One of the plasmacytomas possessed clearly detectable surface immunoglobulin. All three lacked the receptors for Fc and C3.

2150 NASOPHARYNGEAL CARCINOMA V: IMMUNOGENETIC STUDIES OF SOUTHEAST ASIAN ETHNIC GROUPS WITH HIGH AND LOW RISK FOR THE TUMOR. (E.)

Simons, M. J. (WHO Immunology Res. Training Ctr., Singapore, Malaysia), N. E. Day, G. B. Wee, K. Shanmugaratnam, H. C. Ho, S. H. Wong, T. K. Ti, N. K. Yong, S. Darmalingam and G. de-The. *Cancer Res* 34(5):1192-1195, 1974.

One hundred forty-four Chinese patients with nasopharyngeal carcinoma (NPC), 148 normal Chinese, and 88 patients, suspected on clinical grounds of having NPC but in whom no evidence of cancer was seen in histological preparations of biopsy tissue and who were therefore presumed to be free of NPC, were studied for *HL-A* antigen patterns. The antisera used identified up to eight 1st-locus and up to 14 2nd-locus specificities. The two major findings in the NPC patients were a significantly increased frequency of *HL-A2* and a nonspecific deficit of 2nd-locus antigens. The proportion of patients with the high-risk characteristic (*HL-A2*; <two 2nd-locus antigens) versus low-risk individuals (lacking *HL-A2*; two 2nd-locus antigens) differed between the NPC patients and the comparison groups to a high order of statistical significance ($\chi^2 = 16.15$; $p = 0.00006$; relative risk = 4.5).

2151 CARCINOEMBRYONIC ANTIGEN AND ALPHA-FETO-PROTEIN IN THE DIAGNOSIS OF GASTRIC AND COLONIC CANCER: A COMPARATIVE CLINICAL EVALUATION. (E.)

Ravry, M. (Mayo Clin., Rochester, Minn.), K. R. McIntire, C. G. Moertel, T. A. Waldmann, A. J. Schutt and V. L. W. Go. *J Natl Cancer Inst* 52(3):1019-1021, 1974.

Serum carcinoembryonic antigen (CEA) and alpha-feto-protein (AFP) levels were simultaneously measured in 100 colorectal cancer patients and 45 gastric cancer patients. In the case of colorectal patients,

the combined assays did not significantly improve diagnostic sensitivity. On the other hand, among 37 gastric cancer patients with distant metastasis, 9 had abnormal CEA and 12 had abnormal AFP. The combined assays, therefore, raised diagnostic sensitivity to 20 of 37, or 54%. In both colorectal and gastric carcinoma patients, elevation of AFP seemed independent of the presence of absence of liver metastasis. The combined determination of serum CEA and AFP can significantly increase the detection rate of metastatic gastric carcinoma.

2152 SEARCHING FOR HUMAN TUMOR ANTIGENS. (E.)

Anderson, N. G. (Mol. Anat. Program, Oak Ridge Natl. Lab., Tenn.), D. W. Holladay, J. E. Caton, E. L. Candler, P. J. Dierlam, J. W. Eveleigh, F. L. Ball, J. W. Holleman, J. P. Breillatt and J. H. Coggin, Jr. *Cancer Res* 34(8):2066-2076, 1974.

This paper discusses theoretical considerations leading to recognition of the importance of the isolation and characterization of human tumor-associated antigens (especially autoantigens) as central problems in cancer research and presents a report on progress made in attempts to develop the concepts and methods required to solve these problems. Aside from tumor and tissue extracts, five main sources of tumor antigens are considered: the isolated tumor cell membrane, the medium in which tumor cells have grown, serum from tumor patients, the human kidney (from which antigen-antibody complexes may be eluted), and urine from tumor patients. Methods of recovering and concentrating both particulate and soluble fractions are discussed. For separation of soluble materials, the development is charted of automated immunospecific methods, and examples are given of separations achieved. The preparation and rationale of use of cascade systems for removing normal substances in the search for abnormal ones are discussed, and the scope of the methods is indicated.

2153 ESCAPE FROM IMMUNE DESTRUCTION BY THE HOST THROUGH SHEDDING OF SURFACE ANTIGENS: IS THIS A CHARACTERISTIC SHARED BY MALIGNANT AND EMBRYONIC CELLS? (E.)

Alexander, P. (Chester Beatty Res. Inst., Surrey, England). *Cancer Res* 34(8):2077-2082, 1974.

The hypothesis is advanced that macromolecules normally found only in embryonic and fetal cells are also found in tumors because malignant cells, like the fetus, must develop mechanisms to avoid immunological destruction by the host. While anatomical factors play an important role in the "escape" of the fetus as well as the tumor, they are not by themselves adequate. In tumors, the shedding of antigens in a soluble form provides powerful protection because such antigens compete with the tumor for the effector processes of the immune response. Soluble antigens form adducts with antibodies as well as cytotoxic cells, which are then no longer capable of killing the tumor cells. Evidence is presented that the rate of spontaneous shedding of antigen may determine in part the growth pattern of the tumor *in vivo*. Sarcoma cells, which shed antigen rapidly,

metastasize more readily than those with a slow spontaneous release of antigen. It is proposed that rapid shedding of transplantation antigens is a characteristic of embryonic cells and tumors.

- 2154 A COMPARISON OF ENZYME-ACTIVE MEMBRANE ANTIGENS FROM TWO DIFFERENT 4-DIMETHYL-AMINOAZOBENZENE-INDUCED RAT HEPATOMAS WITH THOSE OF ADULT AND FETAL RAT LIVER. (E.) Raftell, M. (Wenner-Gren Inst., U. Stockholm, Sweden), F. Blomberg and P. Perlmann. *Cancer Res* 34(9):2300-2306, 1974.

The differences in the pattern of enzyme-active antigens in the membranes of two different 4-dimethyl-aminoazobenzene-induced rat hepatomas (D23 and D33) were compared with those found in the membranes of normal adult and fetal liver cells. Only one of the nine immunologically different esterase-active antigens present in the adult liver microsomes was also detected in the D23 and D33 microsomes. The plasma membrane fractions of the two hepatomas contained one esterase which differed from the microsomal and liver plasma membrane antigens. Multienzyme complexes containing nucleoside di- and triphosphatase (NDP-NTPase), acid phosphatase, reduced nicotinamide adenine dinucleotide-neotetrazolium reductase activities were seen in the microsomal fractions from both hepatomas; similar complexes were also detected in the plasma membrane fractions of the tumors. One NDP-NTPase-active antigen typical for fetal liver was also found in the D23 and D33 microsomes, but only a few of the multienzyme complexes found in membrane extracts of normal adult liver were detected in the hepatomas. Fetal antigens with γ -L-glutamyl- β -naphthylamidase activity were present in the D33 fractions but not in the D23 fractions. The data suggest that similar dedifferentiation events take place during tumorigenesis.

- 2155 BRAIN-ASSOCIATED TUMOUR ANTIGENS DEMONSTRATED BY IMMUNOFLUORESCENCE. (E.)

Toh, B. H. (Monash U. Med. Sch., Melbourne, Australia) and M. N. Cauchi. *Nature* 250(5467):597-598, 1974.

The presence of brain-associated antigens in rat tumor cells and in lymphoid cells was investigated using a heterologous anti-brain serum. The rat tumors studied were: gliomas and schwannomas, spontaneous mammary carcinomas, a squamous cell carcinoma, and Walker carcinoma. Moderate to strong membrane and cytoplasm staining in 100% of cells was observed in all the tumors tested. In all cases, no staining was observed in the parallel control tests with preimmune serum, absorbed in the same way as the test serum. The staining of brain sections was inhibited only by serum absorption with brain homogenates pointing to the presence of an organ-specific brain antigen. The antiserum also stained the surface membranes of 100% of thymocytes, 61% of peripheral blood lymphocytes, and 12% of lymph node cells. It is suggested that there is also a cytoplasmic thymic antigen common to brain and thymus. In addition there seem to be at least two brain-associated tumor antigens: the first is shared by brain and the cell membranes

of tumor cells and thymocytes, and the second is shared by brain and the cytoplasm of the tumor cells investigated.

- 2156 PRESENCE OF A MOUSE EMBRYONIC ANTIGEN ON HUMAN SPERMATOZOA. (E.) Buc-Caron, M.-H. (Pasteur Inst., Paris, France), G. Gachelin, M. Hofnung and F. Jacob. *Proc Natl Acad Sci USA* 71(5):1730-1733, 1974.

A cell-surface antigen common to mouse primitive teratocarcinoma (PTC) cells, morulae, and spermatozoa is specified by the t^{12} allele at the T-locus of the mouse. Quantitative absorptions of anti-PTC-F9-41 cells with increasing amounts of human spermatozoa showed a decrease in cytotoxicity after absorption. When human lymphocytes and fibroblasts were assayed for cytotoxic activity of antiserum against F9, no activity could be detected in either case. Thus, the surface of human lymphocytes and fibroblasts appears to be devoid of detectable antigens able to bind antibodies against F9. Similarly, human fibroblasts, erythrocytes, and lymphocytes were unable to remove any detectable serum activity against either F9 or human spermatozoa; F9 cells and human and mouse spermatozoa all decreased both activities. These data indicate that at least some of the antigenic determinants present on mouse teratocarcinoma cells also exist on the surface of human spermatozoa and that these determinants are not widely distributed among various tissues in man. It is possible that this antigen has a similar function in man as it does in the mouse.

- 2157 PASSIVE TRANSFER OF THE RESISTANCE TO TUMOR WITH RNA. (E.) Fukushima, M. (Hiro-saki U. Sch. Med., Japan), S. Machida, A. Hokama, M. Kojika, T. Nishikawa, A. Kikuchi and Y. Ishikawa. *Tohoku J Exp Med* 112(2):155-163, 1974.

RNA was extracted from the spleen cells of male Donryu rats and adult rabbits which had been immunized with Yoshida sarcoma cells (YS-immune rats and rabbits). Donryu rats were then injected with: RNA from YS-immune rats or rabbits, normal rats or rabbits, or rabbits which had been immunized with normal rat spleen supernatant; RNA which had been pretreated with RNase or DNase; allogeneic spleen or lymphoid cells which had been incubated with RNA; or spleen or lymphoid cells which had been incubated with RNA which had been pretreated with RNase or DNase. Eight days later these animals were inoculated i.p. with 10^5 YS tumor cells. Twenty percent of the animals treated with the YS-immune rat RNA survived following the inoculation of YS tumor cells, while 30% of those treated with the YS-immune rabbit RNA survived. Fifty percent of those treated with lymphoid cells incubated with YS-immune rat RNA survived and 29% of those treated with lymphoid cells incubated with YS-immune rabbit RNA survived. The survival rate was 50% among the animals treated with spleen cells incubated with YS-immune rat RNA and 30% among those treated with spleen cells incubated with YS-immune rabbit RNA. Splenic RNA

from the normal rats and rabbits and from the rabbits sensitized with splenic supernatant from normal rats had no antitumor effect. The antitumor effect of the RNA derived from the YS-immune rats was lost by treatment with RNase, but not DNase; similarly, lymphoid cells incubated with YS-immune RNA pretreated with RNase, but not DNase, had no antitumor effect.

2158 HUMAN IMMUNE RESPONSE TO ACTIVE IMMUNIZATION WITH RAUSCHER LEUKEMIA VIRUS. I. CELL-MEDIATED AND CELL-ASSOCIATED IMMUNITY. (E.)

Hersh, E. M. (U. Texas, Houston, M.D. Anderson Hosp., Tumor Inst.), J. U. Gutterman, G. Mavligit, C. R. Gschwind, E. J. Freireich, P. H. Levine and E. J. Plata. *J Natl Cancer Inst* 53(2):317-325, 1974.

Thirteen patients with solid tumors and seven patients with leukemia were immunized intradermally with formalin-killed Rauscher leukemia virus (RLV). No untoward side effects were noted. The *in vitro* lymphocyte blastogenic responses to the RLV and to the JLV-V9r antigen (isolated from an RLV-infected and -transformed BALB/c mouse cell line) were increased after immunization, indicating the development of cell-mediated immunity. The responsiveness to RLV developed one wk after the first immunization, declined, recovered between the fourth and fifth wk, then declined again. The response to the JLV-V9r antigen was weaker, reaching a maximum during the fourth wk. The optimal stimulatory dose of antigen *in vitro* was 174 µg/ml. The lymphocytes from the immunized patients showed little response to virus-free tissue culture vehicle or to a control antigen preparation from noninfected cells, indicating that the responses were specific for the immunizing viral antigen. About 3/4 of the patients showed a true response to the RLV preparation, and about 1/4 showed a response to the solubilized JLV-V9r antigen. Half of the patients showed a definite delayed hypersensitivity to the RLV preparation after immunization. The lymphocyte responses and delayed hypersensitivity responses were comparable in patients with melanoma and other solid tumors, but patients with leukemia had higher pre-immunization lymphocyte responses. Cultures of lymphocytes from patients receiving bacille Calmette Guérin or chemotherapy had higher pre-immunization responses. The data suggest that patients with metastatic cancer and acute leukemia can mount immune responses to oncogenic viruses.

2159 HUMORAL IMMUNE RESPONSES TO TUMOR-SPECIFIC ANTIGENS IN STRAIN-2 GUINEA PIGS. (E.)

Smith, H. G. (Natl. Cancer Inst., Bethesda, Md.) and E. J. Leonard. *J Natl Cancer Inst* 53(1):187-194, 1974.

Serum antibody against tumor-specific antigens was demonstrated on the surface of line-10 guinea-pig hepatoma cells by equilibrating serum with viable tumor cells and detecting bound antibody by indirect immunofluorescence. Summation of the fluorescence intensity grades of individual cells led to a semi-quantitative assay of antibody activity which was sufficiently precise for studies on the magnitude and time course of the antibody response. Antibody

was found not only in guinea pigs immunized against line-10 tumor with a line-10 Bacille Calmette-Guérin (BCG) vaccine, but also in animals with progressively growing and metastasizing tumors. All animals studied had a primary humoral response to line-10 BCG vaccine and generally developed higher antibody levels after multiple inoculations of tumor cells. Immunization with line-10 antigen extracts in complete Freund adjuvant produced delayed cutaneous hypersensitivity responses, but no humoral antibody was detected until after challenge with viable tumor cells, when an apparent anamnestic antibody response was seen. Guinea pigs with progressively growing line-10 tumors developed antibody after 4-5 wk of tumor growth. Before antibody was detected, their serum inhibited the binding of antitumor antibody to line-10 cells.

2160 SUPPRESSION OF *IN VIVO* GROWTH OF MOUSE MYELOMAS BY PURIFIED RABBIT ANTIBODIES AGAINST MOUSE MYELOMA CELLS. (E.)

Yutoku, M. (U. Osaka Med. Sch., Japan), A. L. Grossberg and D. Pressman. *J Natl Cancer Inst* 53(1):201-207, 1974.

The effects of antibodies against myeloma cell-surface antigens on the *in vivo* growth of different myeloma lines were studied. The antibodies were prepared by immunizing rabbits with BALB/c mouse myeloma cells - either MOPC-104E (an IgM-producing line) or MOPC-21 (an IgG-producing line) - and purified by passing through normal BALB/c mice. The anti-MOPC-104E-cell antibodies strongly inhibited the growth of homologous MOPC-104E myelomas in female BALB/c mice. As expected from their cytotoxic reactivity *in vitro*, they also moderately suppressed the growth of Adj-PC-5 (an IgG-producing line) and Akj-PC-22A (an IgA-producing line) myelomas. However, they enhanced the growth of MOPC-21 cells, which were only weakly sensitive to the *in vitro* cytotoxicity of anti-MOPC-104E-cell antibodies. Anti-MOPC-21-cell antibodies suppressed the growth of MOPC-104E and Aje-PC-22A but did not inhibit the growth of the BALB/c mouse lymphoma P1798. Although moderately cytotoxic *in vitro* for the rapidly growing, homologous MOPC-21 cells, anti-MOPC-21 cell antibodies did not suppress the growth of the myeloma *in vivo* under the injection schedule used to suppress growth of the slower growing MOPC-104E and Adj-PC-22A myelomas.

2161 CARCINOEMBRYONIC ANTIGEN BY RADIOIMMUNOASSAY IN THE DETECTION OF RECURRENCE DURING LONG-TERM FOLLOWUP OF FEMALE GENITAL CANCER. (E.)

Khoo, S. K. (U. Queensland, Dept. Obstet., Gynecol., Australia) and E. V. MacKay. *Cancer* 34(3):542-548, 1974.

Seventy-five patients with carcinoma *in situ* of the cervix, invasive carcinoma of the cervix, carcinoma of the endometrium, carcinoma of the ovary, or carcinoma of the vulva were treated surgically. They were then followed up on a long-term basis, with periodic serum carcinoembryonic antigen (CEA) evaluations by microradioimmunoassay and independent assessments of disease status (free of disease, residual disease, or recurrence of disease). The

majority of patients who remained free of disease showed a rapid disappearance of serum CEA after treatment, whereas those who had residual disease continued to show persistence of CEA in the serum. The patients who showed recurrence of the disease showed a reappearance of CEA after an initial disappearance; the mean time interval between reappearance of CEA and detection of the clinical recurrence was 10.7 wks. Thus, although there are limitations to the application of the present radioimmunoassays for CEA, they represent a valuable aid to cancer detection and to the prompt recognition of recurrence during the long-term management of cancer. There is some justification for the institution of earlier treatment for recurrent cancer before it becomes clinically apparent, using estimations of serum CEA.

2162 HL-A ANTIGENS ON CELLS ISOLATED FROM MALIGNANT AND NONMALIGNANT LYMPH NODES. (E.)

Naeim, F. (U. California Sch. Med., Los Angeles), A. Stoddard, G. S. Smith and R. L. Walford. *Tissue Antigens* 4(2):166-171, 1974.

The HL-A profiles of the lymph node cells and peripheral lymphocytes of two patients with carcinoma without lymph node involvement, one patient with lymphadenitis, three patients with Hodgkin's disease, and four patients with other forms of lymphoma were compared. In each case, the HL-A antigens found on the peripheral lymphocytes were also present on the lymph node cells. In addition the lymph node cells and lymphocytes from each patient always reacted with the same individual sera. No significant differences were noted in the HL-A reactivity of the peripheral lymphocytes compared with the lymph node cells from any of the 10 patients.

2163 ANTIBODIES TO EPSTEIN-BARR VIRUS AND SOME OTHER HERPESVIRUSES IN PATIENTS WITH SARCOIDOSIS, PULMONARY TUBERCULOSIS AND ERYTHEMA NODOSUM. (E.) Nikoskelainen, J. (Dept. Virol., U. Turku, Finland), M. Hannuksela and T. Palva. *Scand J Infect Dis* 6(3):209-216, 1974.

Immunofluorescence (IF) and immunodiffusion (ID) techniques were used to examine the sera of 120 patients with sarcoidosis, 21 patients with pulmonary tuberculosis, and 25 patients with nonsar-coid erythema nodosum for antibodies to Epstein-Barr virus (EBV). Sera from healthy donors of the same age and sex as the sarcoidosis and erythema nodosum patients were also examined. In addition, complement fixing (CF) antibodies to herpes simplex (HSV), varicella-zoster (VZV), and cytomegalovirus (CMV) were studied. EVB IF antibodies were found in 97.5% of the sarcoidosis and matched control sera. However, the sarcoidosis patients had high EBV IF titers (640) and strong ID reactions (grade 2-3) significantly more often than the matched controls. Antibody titers to HSV and VZV, but not to CMV, were also higher among the sarcoidosis patients than the controls. The EBV antibody levels were also elevated (compared with the controls) in the pulmonary tuberculosis patients; the antibody titers

to the other herpesvirus were within normal limits in these patients. Compared with the controls, the antibody titers to all herpesviruses were within normal limits in the nonsar-coid erythema nodosum patients. Although most sarcoidosis patients have higher EBV antibody titers than healthy controls, an etiologic role of EBV in sarcoidosis seems improbable on the basis of these data.

2164 INTERRELATIONSHIP OF CARCINOEMBRYONIC ANTIGEN AND COLON CARCINOMA ANTIGEN-III. (E.)

Newman, E. S. (Hoffmann-LaRoche, Inc., Nutley, N.J.), S. E. Petras, A. Georgiadis and H. J. Hansen. *Cancer Res* 34(8):2125-2130, 1974.

For the preparation of carcinoembryonic antigen from 0.5-5.0 kg of liver metastasis of colon carcinoma, a method is described which includes extraction with perchloric acid, column chromatography with the use of mixed-bed ion-exchange cellulose, and gel filtration. Carcinoembryonic antigen isolated from different individual tumors was interchangeable in radio-immunoassay and demonstrated homology of the protein moiety, while differences in the carbohydrate portion are probably due to damage caused by autolysis. An additional step was required in the preparation of colon carcinoma antigen-III; polyacrylamide electrophoresis appeared to yield purified antigen. A comparison of the immunological and chemical properties of carcinoembryonic antigen *versus* those of colon carcinoma antigen-III showed them to be closely related glycoproteins which do not cross-react in radioimmunoassay. A radioimmunoassay was developed to determine colon carcinoma antigen-III concentration, and the normal titer in plasma ranges from 0.7-1.5 µg/ml.

2165 NEOANTIGENS ON SPONTANEOUS AND CARCINOGEN-INDUCED RAT TUMOURS DEFINED BY *IN VITRO* LYMPHOCYTOTOXICITY ASSAYS. (E.) Baldwin, R. W. (Cancer Res. Campaign Labs., U. Nottingham, England) and M. J. Embleton. *Int J Cancer* 13(4):433-443, 1974.

Lymph-node cells from rats of an inbred Wistar strain bearing tumors apparently lacking in tumor rejection antigens were cytotoxic *in vitro* for cultured tumor cells. Tumors studied included mammary carcinomas (6), sarcomas (3), epithelioma (1), and squamous cell carcinoma arising in the external ear duct (1). The specificity of the cytotoxic reactions differed, however, from those demonstrated immunogenic chemically-induced rat tumors since cross-reactivity was observed, especially between tumors of the same histological type. This was most clear in tests with rat mammary carcinomas where tumor-bearer lymph-node cells were cytotoxic for a range of mammary carcinomas including spontaneously arising and chemically induced tumors. The reactivities of tumor-bearer lymph-node cells could be blocked by pretreating target cells with serum of tumor-bearing rats and also by sera of multiparous rats. Conversely, tumor-bearer sera were highly effective in blocking embryo cells from attack by sensitized lymph-node cells from multiparous rats. These results suggest that antigens detected on these tumors by the *in vitro*

assay were embryonic components which were immunogenic in the tumor-bearing host, although they were not capable of inducing tumor-rejections in immunized rats.

- 2166 COMPARISON OF ANTIGENICITY OF HEPATOMA CELLS, NORMAL LIVER CELLS, FOETAL LIVER CELLS AND CHEMICALLY DAMAGED LIVER CELLS IN GUINEA-PIGS IMMUNIZED WITH HEPATOMATA USING THE MACROPHAGE MIGRATION INHIBITION TEST. (E.) Desai, H. N. (Dept. Pharmacol., U. Coll. London, England) and M. M. Dale. *Br J Cancer* 30(2):109-117, 1974.

The macrophage migration inhibition test was used to study the immune responses of guinea-pigs immunized with injections of whole cells of both an allogeneic and a syngeneic hepatoma grown as established cell lines in tissue culture. A clear dose-response relationship between tumor cell concentration and migration inhibition was seen in immunized animals and no significant migration inhibition was seen in control animals. There was no cross reaction between the two tumors used. There was no cross reaction between whole isolated normal liver cells and tumor cells, or between fetal liver cells and tumor cells. Whole isolated liver cells from carbon tetrachloride damaged livers caused some degree of migration inhibition in both normal and immunized guinea-pigs but they did not appear to cross react with hepatoma cells.

- 2167 ISOLATION OF EMBRYONIC ANTIGENS FROM CHEMICALLY INDUCED RAT HEPATOMAS. (E.) Price, M. R. (Cancer Res. Campaign Lab., U. Nottingham, England). *Biochem Soc Trans* 2(4):650-652, 1974.

Tumor-associated embryonic antigens were purified from the cytoplasm of two chemically induced hepatomas (D23 and D30) maintained by serial transplantation in syngeneic Wistar rats. The purified antigens retained the capacity to neutralize the membrane immunofluorescence staining by multiparous rat sera of surface antigens expressed in either D23 or D30 cells, thus confirming the cross-reactive nature of these embryonic antigens. The purified fractions from D23 and D30 gave single bands upon electrophoresis on polyacrylamide gels. There were no significant differences in electrophoretic mobilities of the two antigen preparations. The molecular wt of the D23 and D30 antigens was estimated at 65,000-70,000. These studies thus show that it is possible to isolate tumor-associated embryonic antigens as relatively homogeneous products.

- 2168 AN ANTIGEN IN HODGKIN'S DISEASE TISSUE CULTURES: RADIOIODINE-LABELED ANTIBODY STUDIES. (E.) Long, J. C. (Huntington Mem. Hosp., Boston, Mass.), A. C. Aisenberg and P. C. Zamecnik. *Proc Natl Acad Sci USA* 71(7):2605-2609, 1974.

An antiserum was prepared in rabbits against an antigen obtained by density gradient sedimentation of centrifuged medium from monolayer cultures of spleens involved by Hodgkin's disease. The antiserum was tested by isotopic antibody techniques with cells

from each of eight cultures derived from spleens involved by Hodgkin's disease, four cultures derived from normal adult spleen, and one culture each of fetal spleen and thymus. By an indirect radioiodine-labeled antibody assay, anti-Hodgkin's disease globulin reacted with an antigen on the surface of cells from the Hodgkin's disease cultures, the quantity of which was related to the number of target cells and the amount of antibody used. This Hodgkin's disease tissue culture antigen did not react with a rabbit antiserum against fractionated medium from a normal spleen culture, nor against noncultured Hodgkin's disease tumor tissue. The tumor specificity of the Hodgkin's disease tissue-culture antigen was assessed by a direct technique using ^{125}I -labeled anti-Hodgkin's disease globulin absorbed with either cultured Hodgkin's disease cells or with cultured normal cells. The quantity of antigen on cells from Hodgkin's disease cultures was 15- to 30-fold greater than that on cells from normal cultures.

- 2169 CIRCULATING CARCINOEMBRYONIC ANTIGEN LEVELS AND SERUM SUPPRESSION OF PHYTOHEMAGGLUTININ-STIMULATED LYMPHOCYTE DNA SYNTHESIS: AN INVERSE CORRELATION IN THE CANCER PATIENT. (E.) Steward, A. M. (Boston City Hosp., Mass.), H. Z. Kupchik and N. Zamcheck. *J Natl Cancer Inst* 53(1):3-9, 1974.

Twenty-three patients with digestive tract cancer and 13 patients with breast cancer were studied to determine the relationship between circulating carcinoembryonic antigen (CEA) levels and the suppressive activity of their sera on phytohemagglutinin-induced DNA synthesis in normal human lymphocytes. Ten of the 11 patients with metastases had positive serum CEA levels ($>2.5 \text{ ng/cm}^3$), but only two had sera which inhibited normal DNA synthesis to $<80\%$ of control values. Of 25 patients with primary disease and without known metastases, nine had positive serum CEA levels, and 14 had suppressive sera. After the primary tumor was resected, inverse changes in the CEA and suppressive levels occurred. This change suggests a functional immunologic relationship between serum-suppressive activity and CEA.

- 2170 PHASE-SPECIFIC ONCOCOLON ANTIGENS: A THEORETICAL FRAMEWORK FOR "CARCINOEMBRYONIC ANTIGEN" SPECIFICITIES. (E.) Rule, A. H. (Tufts U. Sch. Med., Boston, Mass.) and C. Goleski-Reilly. *Cancer Res* 34(8):2083-2087, 1974.

The zirconyl phosphate gel radioimmunoassay for the carcinoembryonic antigen (CEA) was applied to various 0.9% NaCl solution extracts of entodermally derived human tumors, fetal gut, meconium, and normal colon fractions separated by ampholine isoelectric focusing in 7 M urea. Comparison of the $A_{280 \text{ nm}}$, pH, and CEA radioimmunoassay "fingerprints" obtained has permitted the reconstruction of a system of phase-specific derepressive, dedifferentiating steps in antigen expression of entodermal oncogenesis. Such data suggest enhanced synthesis of CEA-reacting molecules present early in fetal life which persist throughout adulthood (autoantigens); the presence

of an oncofetal colon antigen which hits antigenic ascendancy the last trimester of fetal life (the pH 3 antigens); and the presence of an oncoembryonic antigen which dominates early in the first trimester of life *in utero* (the pH 4 antigen). Preliminary findings also suggest that the oncofetal colon, pH 3 antigen may play an important role in mediating immune surveillance in patients with Crohn's disease. The data help to explain the broad diagnostic scope of the present plasma CEA radioimmunoassay clinical results and suggest the need to develop and test newer radioimmunoassays for phase-specific oncocolon antigens.

- 2171 SUBCELLULAR REPRESENTATION OF MURINE THYMUS-LEUKEMIA (TL) ANTIGENS IN PHENOTYPICALLY TL⁺ AND TL⁻ CELLS. (E.) Smith, S. R. (New York U. Sch. Med., New York), M. E. Lamm, M. L. Powers and E. A. Boyse. *J Immunol* 113(4):1098-1106, 1974.

The subcellular representation of thymus-leukemia (TL) antigens in murine cells was studied by inhibition of cytotoxic antiserum. By differential centrifugation, subcellular fractions were obtained from six sources: thymocytes of B6 mice (TL⁻); thymocytes of a congenic mouse line (B6-TL⁺) differing from B6 at the Tla locus; a TL⁺B6 leukemia (ERLD); a TL⁻B6 leukemia (E⁺G2); and liver cells from B6 and B6-TL⁺ mice. Only fractions obtained from the phenotypically TL⁺ sources contained TL antigen. Plasma membranes were most active, followed by mitochondria and microsomes. Nuclear and cytosol fractions contained no intrinsic activity. These results suggest that the phenotypic expression of TL antigens is not a question of selective expression at the cell surface but reflects instead repression *vs* derepression at the level of the genome.

- 2172 IMMUNE CONTROL OF HERPES SIMPLEX VIRUS INFECTIONS. (E.) Ennis, F. A. (Food Drug Admin., Bethesda, Md.) and M. Wells. *Cancer Res* 34(5):1140-1145, 1974.

The role of cell-mediated protection to herpes simplex infection was studied *in vivo* and *in vitro*. Sensitized spleen cells, obtained from syngeneic mice immunized with herpes simplex virus, protected recipient mice against lethal challenge with herpes simplex virus. Survival was significantly greater in challenged mice that received washed spleen cells from donor animals immunized with herpes simplex than from control donor animals. This increase in survival after challenge was associated with a significant decrease in virus titers in the brains of mice that had received specifically sensitized cells. There was no obvious association between increased survival and the levels of serum antibody and interferon in the challenged animals. *In vitro* studies demonstrated control of herpes simplex infection in human and murine cell cultures by sensitized spleen cells from specifically immunized mice. Control of infection required intact, immune, non-glass-adhering lymphoid cells.

- 2173 EXPRESSION OF MAMMARY TUMOR VIRUS ANTIGEN ON THE MEMBRANES OF LYMPHOID CELLS. (E.) Gillette, R. W. (Meloy Labs., Springfield, Va.), S. Robertson, R. Brown and K. E. Blackman. *J Natl Cancer Inst* 53(2):499-505, 1974.

An indirect immunofluorescent technique and a ⁵¹Cr release toxicity assay were used to detect mouse mammary tumor virus (MMTV) antigens on BALB/c, C57BL/6, RIII, C3H/He, DD/He, AKR, and NIH Swiss mouse lymphoid cells. MMTV expression was greatest in lymphoid cells of splenic, lymph node, and peritoneal origin. The quantitative levels of surface antigen expression in these cells correlated strongly with the levels of virus excretion in milk and mammary tumor formation in high-virus expressor strains such as C3H/HeN, RIII, and DD/He. The percentage of MMTV-positive lymphoid cells increased with the age of the animal; it rose markedly shortly after birth in all strains, but reached higher levels earlier in the strains with the greatest natural mammary tumor incidence. All strains examined expressed MMTV cell-surface antigen, but the low-expressor strains expressed it at markedly lower levels. The relative absence of MMTV in the thymus, the pattern of distribution in other lymphoid organs, and the sensitivity of positive cells to anti-IgM and anti-MMTV but not anti- θ serum suggested that MMTV structural components were expressed on the lymphoid cells and that this was associated primarily with the bone marrow-derived lymphocytes.

- 2174 PROPERTIES OF THE COMMON ANTIGEN ASSOCIATED WITH MAREK'S DISEASE HERPESVIRUS AND TURKEY HERPESVIRUS INFECTIONS. (E.) Onuma, M. (Sapporo Med. Coll., Japan), T. Mikami and T. T. A. Hayashi. *J Natl Cancer Inst* 52(3):805-813, 1974.

An agar-gel precipitation (AGP) antigen prepared from feather tips of chickens infected with Marek's disease herpesvirus (MDHV), and four antigens from cell extracts or culture fluids of cultures infected with either MDHV or herpesvirus of turkeys (HVT) had one precipitation line in common. The common antigen was stable at 50 C, but not 60 C, for 30 min, unstable at pH 10.5 or above, or pH 2.5 or below, and remained in the aqueous phase after centrifugation at 100,000 x g for 90 min. It was unaffected by acetone and ether, but was partially destroyed by pronase and completely by sodium periodate. These findings suggest that the common antigen obtained from the cells with MDHV or HVT was a glycoprotein. The possibility that it is associated with the envelope of the virus is discussed.

- 2175 REACTIVITY OF ENVELOPE, CAPSID, AND SOLUBLE ANTIGENS OF HERPESVIRUS HOMINIS TYPES 1 AND 2 IN THE INDIRECT HEMAGGLUTINATION TEST. (E.) Back, A. F. (California State Dept. Hlth, Berkeley) and N. J. Schmidt. *Infect Immun* 10(1):102-106, 1974.

Envelope, capsid, and soluble antigens of *Herpesvirus hominis* (HVH) types 1 and 2 were compared with crude antigens (from disrupted HVH-infected HeLa

cells) in terms of potency, type-specificity, and diagnostic value in the indirect hemagglutination (IHA) test. The envelope antigen appeared to be the predominant component reacting in the IHA test, but recurrent HVH infections increased the reactivity of human sera with capsid antigens. The soluble antigens reacted in the IHA test with HVH immune animal sera, but few convalescent-phase human sera showed reactivity with the soluble antigens. Overall, none of the subunit antigens showed greater type-specificity than the crude antigens in IHA tests with immune animal and convalescent-phase human sera. Recurrent infections with type 1 or type 2 viruses tended to broaden heterotypic reactivity of the patients' sera with both crude and subunit antigens, even in patients showing only a single type of antibody by IHA inhibition. Subunit antigens were no more sensitive than crude antigens in demonstrating significant IHA antibody titer rises for serodiagnosis of herpesvirus infections, they generally had to be used at lower working dilutions than the crude antigens. The results indicate that both common and type-specific HVH antigens are present in the envelope, and perhaps in the capsid and that the development of antigens for the direct typing of HVH antibodies will depend on further separation of the specific type 1 and type 2 components from the common antigens.

- 2176 ALTERATIONS OF THE IMMUNOLOGICAL SPECIFICITY OF PLASMA MEMBRANES FROM CELLS INFECTED WITH MAREK'S DISEASE AND TURKEY HERPES VIRUS. (E.) Kaaden, O. R. (Federal Res. Inst. Animal Virus Dis., Tubingen, W. Germany) and B. Dietzschold. *J Gen Virol* 25(1):1-10, 1974.

Highly purified plasma membranes were isolated from chicken embryo fibroblasts infected with Marek's disease virus (MDV) or turkey herpes virus (HVT). Polyacrylamide gel electrophoresis showed that the membrane preparations contained two new virus-induced polypeptides. When reacted in the double immunodiffusion test, solubilized plasma membranes from MDV-infected cells formed two specific precipitation bands with Marek's disease immunoglobulins. Antisera prepared against plasma membranes from MDV- or HVT-infected cells neutralized extracellular infectious HVT. The Marek's disease mortality of chickens twice vaccinated with a plasma membrane preparation from HVT-infected cells was reduced by 94%. From the results it was concluded that the plasma membranes acquire new immunologic specificities after infection with MDV or HVT.

- 2177 ALVEOLAR CELL CARCINOMA-LIKE ANTIGEN AND ANTIBODIES IN PATIENTS WITH ALVEOLAR CELL CARCINOMA AND OTHER CANCERS. (E.) Mohr, J. A. (U. Oklahoma Hlth. Sci. Ctr., Oklahoma City), R. E. Nordquist, E. R. Rhoades, R. E. Coalson and J. J. Coalson. *Cancer Res* 34(8):1904-1907, 1974.

Antiserum was produced in sheep against a particle pellet recovered from human alveolar cell carcinoma (ACC). The antiserum was used for the detection of similar antigens in patients with ACC using the im-

munodiffusion method. Tumor cell lines were used in the indirect fluorescent technique for the detection of antibodies in the serum of patients with tumors and control serum. Similar antigens were present in the serum of 9 of 18 patients with ACC, 3 of 4 with primary lung adenocarcinoma, and 2 of 18 with Hodgkin's disease. Antibodies developed in 11 of 13 tested patients with ACC, 3 of 5 with primary lung adenocarcinoma, and in sheep inoculated with the agent.

- 2178 TUMOR-ASSOCIATED ANTIGEN (TAA) AND ANTI-TAA ANTIBODIES IN THE SERUM OF BALB/c MICE WITH PLASMACYTOMAS. (E.) Kolb, J. P. (Inst. Sci. Res. Cancer, Villejuif, France), M. F. Poupon and G. Lespinats. *J Natl Cancer Inst* 52(3):723-727, 1974.

Sera from BALB/c mice bearing plasmacytomas were studied for the possible presence of soluble tumor-associated antigen (TAA) and anti-TAA antibodies. The antibodies were detected by passive hemagglutination, sheep RBC being sensitized by a soluble tumor extract as a source of antigen. TAA was detected by inhibition of the hemagglutination of a syngeneic antitumor immune serum. Sera were hemagglutinating (antibody activity), inhibitory (antigen activity), or neutral. Preliminary data indicate that inhibitory sera, containing an excess of antigen, are most frequently associated with large tumors, and that the hemagglutinating sera are more often associated with small tumors. The number of cases studied, however, is still too small to establish a statistical correlation between the size of tumor and the activity of serum.

- 2179 CHANGES IN CELL MEDIATED IMMUNE FUNCTIONS BY GROWING TUMOR. (E.) Chaput, B. (Inst. Cancer Res., U. Vienna, Austria), W. Rella and M. Vetterlein. *Eur J Cancer* 10(3):185-188, 1974.

Female Sewall-Wright strain 2 guinea pigs (4- to 6-month-old) were injected i.m. with 300,000 cells of the transplantable adenocarcinoma hepatoma line 1. Five days later, a series of four intradermal immunizations with living tumor cells was begun. At specific time intervals thereafter, the antitumor response was assessed by measuring tumor growth, delayed hypersensitivity reactions at the site of intradermal immunization, *in vitro* stimulation of peritoneal exudate cells (PEC) with tumor cells, and *in vitro* PEC-mediated cytotoxicity. The capability of the specific cell-mediated immune response correlated negatively with the tumor burden imposed on the body's immune system. The animal could respond if the tumor was small, but as the tumor mass exceeded 1 cm in diameter, the immune response decreased strikingly and even became negative. The specificity of the phenomenon was checked by the ability of the spleen of such animals to produce plaque-forming cells (PFC) against sheep red blood cells. No decline in reactivity was seen in the PFC response, indicating that general immune reactivity was retained even in otherwise nonreactive animals.

(2180-2184)

- 2180 THE REACTION BETWEEN CARCINOEMBRYONIC ANTIGEN AND CONCAVALIN A. (E.) Chu, T. M. (Roswell Park Mem. Inst., Buffalo, N. Y.), E. D. Holyoke and G. P. Murphy. *Cancer Res* 34(1):212-214, 1974.

The binding reaction between carcinoembryonic antigen (CEA) and concanavalin A (Con A) was studied. CEA, prepared from liver metastases in patients with carcinoma of the colon, was tested against Con A for precipitation. Using the techniques of immunodiffusion and counter-electrophoresis, a precipitate line between CEA and Con A was observed, which was different from that seen between either Con A-anti-Con A or CEA-anti-CEA. CEA could be bound by Con A in solution using the double antibody technique. However, Con A did not inhibit the titration reaction of CEA and anti-CEA by Hansen's Z-gel method. Mannose, known to inhibit specific reactions of Con A, inhibited the binding of CEA by Con A. These findings help to characterize the surface structure of the CEA molecule and suggest the potential utilization of Con A and affinity chromatography to isolate CEA.

- 2181 ANTIBODIES TO EPITHELIUM IN BENIGN PROSTATIC HYPERTROPHY AND CARCINOMA OF PROSTATE: EXACERBATION TO HYPERPLASIA AND NEOPLASIA AND POSSIBLE CLUE TO CANCER. (E.) Ablin, R. J. (Cook County Hosp., Chicago, Ill.), P. Guinan and I. M. Bush. *Urology* 3(3):373-375, 1974.

Serum samples were obtained from 42 patients with benign prostatic hypertrophy and 24 patients with carcinoma of the prostate. The latter group had been treated with estrogen administration and/or orchiectomy. Sections of mouse esophagus were treated with the sera and with a fluorescein-labeled antiserum to human immunoglobulin-G. Antibodies in the sera were reactive with four histologically identifiable components of stratified squamous epithelium: basement-membrane zone; cytoplasmic membrane or intercellular areas; keratohyalin granules; and nuclear membrane. The frequency and range in the immunofluorescent-staining titer of antibodies reactive with these epithelial components varied somewhat among the benign prostatic hypertrophy patients and the prostatic carcinoma patients. The data are of interest in view of studies suggesting that cutaneous reactions to an internal malignant condition may antedate the actual identification of malignant neoplasm.

- 2182 USE OF NONHUMAN PRIMATES FOR ASSAYING TUMORIGENICITY OF VIRAL-VACCINE CELL SUBSTRATES. (E.) Petricciani, J. C. (U.S. Food Drug Admin., Bethesda, Md.) and D. P. Martin. *Transplant Proc* 6(2):189-192, 1974.

Anti-African-green antithymocyte globulin (ATG) was injected s.c. into newborn, infant, and juvenile rhesus and African green monkeys before and after KB (human epidermoid carcinoma), WI-38 (diploid human fetal lung), RMK (primary rhesus-monkey kidney), RK (primary rabbit kidney), CE (primary chicken

embryo), DE (primary duck embryo), VMK (primary African-green-monkey kidney), HeLa (human cervical carcinoma), Hep-2 (human laryngeal carcinoma), DBS-FRHL-2 (diploid fetal rhesus lung), or Led-WIDR (human colon adenocarcinoma) cell inoculation. The average skin-allograft survival in rhesus monkeys treated with anti-African-green ATG was 24 days. Grossly visible tumor masses were frequently observed following inoculation of the malignant cell lines. In all animals, the tumor was viable until about 9-16 days after inoculation, after which there was increased encapsulation and lymphocytic infiltration. Complete regression at the site of inoculation occurred within 4-6 wk. None of the cell lines currently used or under consideration for use as substrates for virus-vaccine production showed evidence of tumor formation. Thus, rhesus and African green monkeys can be used successfully to assess tumorigenicity when they are conditioned with ATG.

- 2183 ANTIBODIES TO COMMON OVINE AND BOVINE C-TYPE VIRUS SPECIFIC ANTIGEN IN SERUM FROM SHEEP WITH SPONTANEOUS LEUKOSIS AND FROM INOCULATED ANIMALS. (E.) Paulsen, J. (Inst. Hyg. Infect. Anim. Dis., Justus Liebig U., Giessen, W. Germany), R. Rudolph and J. M. Miller. *Med Microbiol Immunol* 159(2):105-114, 1974.

C-type virus-containing preparations from concanavalin-stimulated sheep lymphocyte culture fluids were treated with ether, and used for antigen in immunodiffusion tests. Thirteen out of 14 sera from sheep with spontaneous lymphatic leukosis showed precipitation reaction with the antigen preparation. Three out of 33 sera from clinically nonsuspect sheep in the same multiple case herd also formed precipitin bands. Three out of 37 sera from offspring of leukotic ewes, three out of nine sera from sheep, inoculated as newborn lambs with leukotic material, and one out of four sera from inoculated goats precipitated in the same manner. Immunodiffusion tests with a similar antigen preparation from bovine lymphocyte culture fluid led to identical results. Sera from 162 sheep in leukosis-free herds did not show precipitation reactions. These findings seem to demonstrate the presence of antibodies to common ether-resistant ovine and bovine C-type virus specific antigen. These investigations show a clear correlation between clinical findings in sheep leukosis, demonstration of C-type particles in lymphocyte cultures, and antibody reactions.

- 2184 MEMBRANE ANTIGEN OF BOVINE PAPILLOMA VIRUS-INDUCED FIBROMA CELLS. (E.) Barthold, S. W. (Dept. Vet. Sci., U. Wisconsin, Madison) and C. Olson. *J Natl Cancer Inst* 52(3):737-742, 1974.

A surface antigen on live, unfixed, bovine papilloma virus-induced fibroma cells was demonstrated with the indirect immunofluorescence (IF) test. Sera from six calves (out of seven inoculated) with experimentally produced fibromas contained antibody to cultured fibroma cells; this indicated exposure to the same antigen. No activity could be demonstrated with the same sera tested against cultured

normal dermal fibroblasts from the same donor animal. The serum antibody activity could be removed by absorption with tumor cells but not with normal cells. Cultured fibroma cells were negative for viral antigens by the direct IF test and electron microscopic examination. Sequential antibody titers indicated correlation with onset of tumor growth but not with progression or regression of fibromas.

- 2185 IMMUNOLOGICAL REACTIONS TO TUMOR-ASSOCIATED ANTIGENS IN BURKITT'S LYMPHOMA AND OTHER LYMPHOMAS. (E.) Herberman, R. B. (Nat'l. Cancer Inst., Bethesda, Md.), J. L. McCoy and P. H. Levine. *Cancer Res* 34(5):1222-1227, 1974.

Evidence for immune response to Burkitt's tumor and other lymphomas is reviewed. The common tumor-associated antigens detected in some assays and the natural reactivity to some of these antigens are analogous to the findings in virus-induced tumors in experimental animals. Delayed hypersensitivity reactions to autologous tumor extracts were observed in Burkitt's lymphoma, in Hodgkin's disease, and in other lymphomas. Patients with leukemia and lymphoma, but not carcinomas, also reacted with extracts of tumor-derived lymphoid cell lines. Studies of *in vitro* cell-mediated cytotoxicity against autologous tumor cells, using the ^{51}Cr release assay, also gave evidence for reactivity against tumor-associated antigens. In humoral and cell-mediated cytotoxicity assays against lymphoid tissue culture cells, widespread natural reactivity was found. The nature of the antigens detected in these assays is discussed, particularly the possible relationship to Epstein-Barr virus. Delayed skin reactivity to the extracts of lymphoid cell lines was found to correlate with elevated Epstein-Barr virus antibody titers.

- 2186 VARIATION IN QUANTITATIVE EXPRESSION OF FORSSMAN ANTIGEN ON VIRUS-TRANSFORMED HAMSTER CELLS. (E.) G. D. Shantz (Pennsylvania State U. Coll. Med., Hershey) and R. N. Lausch. *J Nat'l Cancer Inst* 53(1):239-246, 1974.

The expression of Forssman antigen on normal and virus-transformed hamster cells was investigated by a complement-dependent microcytotoxicity test. The cell lines varied considerably with respect to the dilution of rabbit anti-sheep erythrocyte serum required to promote lysis. With quantitative absorption procedures, the relative Forssman antigen content of the virus-transformed cells was compared with that of untransformed hamster embryo fibroblasts (HEF) and hamster cells transformed by other agents. These studies indicate that the amount of antiserum needed to promote lysis was inversely proportional to the density of Forssman antigen on the cell surface. HEF preparations tested under confluent or nonconfluent conditions required significantly less antiserum for sensitization than did lines of HEF transformed by herpes simplex virus or PARA-adenovirus 7. The results indicate that virus transformation of these cells is consistently accompanied by a reduction Forssman antigen expression.

- 2187 CELL-MEDIATED IMMUNITY TO FRIEND VIRUS-INDUCED LEUKEMIA. (E.) Ting, C. C. (Nat'l. Cancer Inst., Bethesda, Md.), G. Shiu, D. Rodrigues and R. B. Herberman. *Cancer Res* 34(7):1684-1687, 1974.

A Friend virus-induced leukemia cell line (FBL-3) in C57BL/6 mice, was very tumorigenic when the cells were inoculated i.p.; the dose of cells that produces 50% tumor growth was less than 1×10^1 cells. This cell line was very immunosensitive in tumor transplantation experiments; immunization with leukemias induced by Friend, Moloney, or Rauscher viruses produced more than 4 logs of protection. However, Friend virus-induced leukemia of syngeneic or allogeneic origin gave a higher degree of protection than did the leukemias induced by Moloney or Rauscher viruses, suggesting that Friend virus-induced leukemias possess a unique type-specific (Friend) tumor-associated transplantation antigen, in addition to a common tumor-associated transplantation antigen shared by the leukemias induced by Moloney or Rauscher viruses. The *in vitro* cell-mediated immunity was tested by the ^{125}I -iododeoxyuridine cytotoxicity test. These results parallel the antigenic specificities defined by the serological studies and may also correlate with the *in vivo* tumor transplantation experiments.

- 2188 ANTIBODIES TO HERPES GROUP VIRUSES IN PATIENTS WITH NASOPHARYNGEAL AND OTHER HEAD AND NECK CANCERS. (E.) Henderson, B. E. (U. South. California Sch. Med., Los Angeles), E. Louie, E. Bogdanoff, W. Henle, B. Alena and G. Henle. *Cancer Res* 34(5):1207-1210, 1974.

Epstein-Barr virus (EBV) antibody titers were assayed in serum samples from 31 patients with active and inactive nasopharyngeal carcinoma (NPC). There was a significant increase in the geometric mean titer of antibody to EBV in the NPC cases compared with matched controls. The titers to EBV early antigen were also increased in the NPC cases, both the anti-D and anti-R components being elevated. There was no significant difference in antibody titers to cytomegalovirus, herpes simplex, or varicella between the NPC cases and controls. The highest viral capsid antigen titers among the NPC cases were found among Mexican-Americans and Blacks, while the highest early antigen titers were found among Chinese and Blacks. The lowest mean titers to both viral capsid and early antigens were observed among the White NPC cases. The EBV antibody titer also varied with the stage at diagnosis and activity of the disease, being much higher in active than inactive cases. Elevated EBV titers were also found in white patients with epidermoid cancer of the nasal cavity and hypopharynx.

- 2189 IMMUNOGENIC PROPERTIES OF A SOLUBLE TUMOR-SPECIFIC TRANSPLANTATION ANTIGEN INDUCED BY SIMIAN VIRUS 40. (E.) Drapkin, M. S. (Massachusetts Gen. Hosp., Boston), E. Appella and L. W. Law. *J Nat'l Cancer Inst* 52(1):259-264, 1974.

Soluble tumor-specific transplantation antigen was obtained from dissociated tumor cells of the ascites

or tissue-cultured BALB/c lines (mKSA) transformed by simian virus 40. Immunogenic activity as assayed by tumor rejection was clearly recovered in 50% yield in the crude membrane preparation and in at least 5% yield in the crude soluble preparation. This activity was specific. After chromatography on Sephadex G-150, this activity was preserved. Contrary to other studies, *in vitro* assays of cytotoxicity could not be used to monitor solubilization and purification of this antigen.

- 2190 SITES OF SYNTHESIS OF MURINE RNA TUMOR VIRUS (ONCORNAVIRUS) GROUP-SPECIFIC ANTIGENS. (E.) Pattengale, P. K. (New York U. Sch. Med., N.Y.), H. Ikeda and G. J. Thorbeck. *Cancer Res* 34(4): 810-817, 1974.

Autoradiography of immunoelectrophoretic patterns was used to study sites of synthesis of mammary tumor virus group-specific antigen (MTV-sl) and murine leukemia virus group-specific antigen (MuLV-gsl) protein in C3H and AKR mice of various ages. Synthesis of MTV-sl protein was seen only in the mammary gland of tumor-free late pregnant and lactating C3H mice. In addition, mammary tumors were strongly positive for production of MTV-sl antigen. Production of MuLV-gs protein was found in spleen, thymus, lymph node, placenta, mammary gland, testis, and ovary of nonleukemic AKR, as well as in some testis and ovary cultures of C3H mice. Leukemic ARK lymphoid tissue showed much stronger labeling of MuLV-gs than normal. In general, tissues that tended to have high extract titers for MuLV-gs protein as tested by immunofluorescent absorption also appeared positive with respect to synthesis, but some exceptions in this respect were noted.

- 2191 CELLULAR AND VIRAL ANTIGENS OF BALB/c MYELOMA. (E.) Krueger, R. G. (Mayo Med. Sch., Rochester, Minn.), W. H. Williams and G. C. Miller. *J Natl Cancer Inst* 52(4):1203-1210, 1974.

As detected by immunofluorescent microscopy, BALB/c mice bearing a myeloma and BALB/c mice immunized with irradiated myeloma cells produced immunoglobulin G (IgG) against the tumor cells. The IgG reacted with the nucleus and cytoplasm of the six tumor lines examined but not with a syngenic tumor of BALB/c spleen cells. Three cell types were evident in all tumors: 1) a small cell, staining intensely and uniformly; 2) a large cell, staining weakly; and 3) a cell of intermediate size, staining between the extremes of the small and large cell. IgG from rabbits immunized with gradient-purified myeloma A- and C-type particles gave intense staining with the cytoplasm and nucleus of the small cell, less intense uniform staining with the cytoplasm and particulate staining with the nucleus of the intermediate cell, and weak staining with the cytoplasm of the large cell. The viral antigens within or on the tumor cell stimulated humoral antibodies in tumor-bearing or immunized mice and contributed to the immune response against myeloma cells in tumor-bearing mice.

- 2192 RADIOLABELED ANTITUMOR ANTIBODIES. II. QUANTITATIVE ANALYSIS OF MOLONEY TUMOR ANTIGENS ON MOLONEY LYMPHOMA CELLS (LSTRA). (E.) Nord, S. (Stanford Med. Sch., Calif.) and I. L. Weissman. *J Natl Cancer Inst* 53(1):125-130, 1974.

The interaction between rat anti-Moloney antibodies (α Mo) and Moloney lymphoma cells (LSTRA) was analyzed quantitatively. Radiolabeled anti-Moloney antiserum in a paired radiolabel technique detected about 5×10^4 Moloney antigen-specific sites/LSTRA cell. The calculated average association constant (K_A) for this radiolabeled antibody on the LSTRA cells was $7.8-20 \times 10^7$ liters/mole. However, the above figures underestimate the actual number of sites per cell on those cells which express surface antigens and overestimate their numbers on low expression cells; thus, the average cell might have 82,500 sites/cell. It is also possible that the assumption of one site/antibody is incorrect under certain conditions.

- 2193 ENHANCING T LYMPHOCYTES FROM TUMOR-BEARING MICE SUPPRESS HOST RESISTANCE TO A SYNGENEIC TUMOR. (E.) Treves, A. J. (Weizmann Inst. Sci., Rehovot, Israel), C. Carnaud, N. Trainin, M. Feldman and I. R. Cohen. *Eur J Immunol* 4(11):722-727, 1974.

- 2194 *IN VIVO* AND *IN VITRO* RESPONSES TO TUMOR-ASSOCIATED ANTIGENS: APPARENT ABSENCE OF T CELL PARTICIPATION. (E.) Tyan, M. L. (Dent. Res. Ctr., U. North Carolina, Chapel Hill). *Eur J Immunol* 4(11):727-731, 1974.

- 2195 TRIAL OF RADIOLABELED ANTIBODY LOCALIZATION IN METASTASES OF A PATIENT WITH A TUMOR CONTAINING CARCINOEMBRYONIC ANTIGEN (CEA). (E.) Reif, A. E. (Boston City Hosp., Mass.), L. I. Curtis, R. Duffield and I. A. Shauffer. *J Surg Oncol* 6(2):133-150, 1974.

- 2196 CARCINOEMBRYONIC-LIKE ANTIGEN IN THE URINE OF PATIENTS WITH CARCINOMA OF THE BLADDER AND NORMAL CONTROLS. (E.) Guinan, P. (Cook Cty. Hosp., Grad. Sch. Med., Chicago, Ill.), R. J. Ablin, N. Sadoughi and I. M. Bush. *J Surg Oncol* 6(2):127-132, 1974.

- 2197 COMPARATIVE *IN VITRO* STUDIES OF EFFECTOR CELL DIVERSITY IN THE CELLULAR IMMUNE RESPONSE TO MURINE SARCOMA VIRUS (MSV)-INDUCED TUMORS IN MICE. (E.) Plata, F. (St. Louis Hosp., Paris, France), E. Gomard, J. C. Leclerc and J. P. Levy. *J Immunol* 112(4):1477-1487, 1974.

- 2198 DEMONSTRATION OF A COMPLEMENT INACTIVATOR ON CULTURED CELLS FROM HUMAN MALIGNANT BRAIN TUMOURS. (E.) Othter, K. (Bispebjerg Hosp., Copenhagen, Denmark), K. Hojgaard and E. Dybkjaer. *Acta Neurol Scand* 50(6):681-689, 1974.

- 2199 ANTIBODY-INDUCED CHANGES IN EXPRESSION OF THE H-2 ANTIGEN. (E.) Lesley, J. (Salk Inst. Biol. Studies, San Diego, Calif.) and R. Hyman. *Eur J Immunol* 4(11):732-739, 1974.
- 2200 NORMAL T CELL POPULATION IN CHRONIC LYMPHOCYTIC LEUKEMIA: ANALYSIS OF PHYTOHEMAGGLUTININ DOSE-RESPONSE CURVES. (E.) Ziegler, J. B. (St. Vincent's Hosp., Sydney, Australia), P. J. Hansen, W. A. Davies and R. Penny. *J Reticuloendothel Soc* 16(5):269-275, 1974.
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- 2202 RELATIONSHIP BETWEEN THE CELLULAR AND VIRAL ANTIGENS OF A BALB/c MYELOMA AND MURINE LEUKEMIA VIRUS. (E.) Krueger, R. G. (Mayo Fdn., Rochester, Minn.) and G. C. Miller. *J Natl Cancer Inst* 53(4):997-1004, 1974.
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- 2223 PROTECTIVE AND CELLULAR IMMUNE RESPONSES TO IDIOTYPIC DETERMINANTS ON CELLS FROM A SPONTANEOUS LYMPHOMA OF NZB/NZW F $_1$ MICE. (E.) Sugai, S. (Dept. Med., U. California, San Francisco), D. W. Palmer, N. Talal and I. P. Witz. *J Exp Med* 140(6):1547-1558, 1974.
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- 2234 CELLULAR IMMUNITY IN HUMAN MALIGNANT MELANOMA AND MELANOMA HISTOLOGY. (E.) Cameron-Mowat, D. E. (Dept. Pathol., Dermatol., U. Glasgow, Scotland), A. J. Cochran, R. M. Grant, C. E. Thomas, R. M. Mackie and W. G. S. Spilg. *Br J Cancer* 28(1):77-78, 1973.
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- 2236 ASSESSMENT OF LYMPHOCYTE TRANSFORMATION IN THE PATIENT PRESENTING WITH HODGKIN'S DISEASE. (E.) Denton, P. M. (Roy. Marsden Hosp., Surrey, England) and E. M. Stanley. *Br J Cancer* 28(1):78, 1973.
- 2237 LYMPHOCYTE TRANSFORMATION IN LARGE BOWEL CANCER. I. (E.) Lauder, I. (Roy. Victoria Infirm., Newcastle upon Tyne, England) and G. Bone. *Br J Cancer* 28(1):78-79, 1973.
- 2238 AGGLUTINATION OF NORMAL AND MALIGNANT CELLS BY CONCAVALIN A IN RELATION TO CELL SURFACE STRUCTURE. (E.) Payne, N. E. (Curie Mem. Fdn., Surrey, England), P. Whur and R. T. Robson. *Br J Cancer* 28(1):86, 1973.
- 2239 INTRALESIONAL BCG IN RECURRENT MELANOMA. (E.) Bornstein, R. S. (Temple U. Sch. Med., Philadelphia, Pa.). *Cancer Cytol* 13(1), 1973.
- 2240 DEMONSTRATION OF A TUMOR-SPECIFIC ANTIGEN, SHARED BY TEN HUMAN TUMORS. (E.) Carvajal, G. (Natl. Polytech. Inst., Mexico City, Mexico), G. Alvarez-Fuertes, R. Medina-Santillan and M. Suarez-Alvarado. *Cancer Cytol* 13(1), 1973.
- 2241 IMMUNOPROPHYLAXIS OF BCG VACCINE ON LEUKEMIA MORTALITY. A RETROSPECTIVE STUDY IN CHICAGO. (E.) Crispin, R. G. (U. Illinois, Med. Ctr., Chicago). *Cancer Cytol* 13(1), 1973.
- 2242 PRODROMAL DYSIMMUNITY IN CANCER. (E.) DeCarvalho, S. (Belmont Med. Clin., Bellflower, Calif.). *Cancer Cytol* 13(1), 1973.
- 2243 USE OF THE LEWIS CRP GEL DIFFUSION TEST IN THE SEROLOGIC DETECTION OF CANCER. (E.) Lewis, A. J. (Lewis Lab., Shaker Heights, Ohio), N. H. Daily and H. A. Killian. *Cancer Cytol* 13(1), 1973.
- 2244 TUMOR ASSOCIATED ANTIGEN STUDIES ON PATIENTS WITH LUNG CARCINOMA USING A THREE LAYER BRIDGE IMMUNOPEROXIDASE TECHNIQUE. (E.) Lo Gerfo, P. (Coll. Phys. Surg., Columbia U., New York, N.Y.), S. Bennett and V. Li Volsi. *Cancer Cytol* 13(1), 1973.
- 2245 CELL-MEDIATED IMMUNE REACTIONS *IN VITRO* AGAINST A CHEMICALLY-INDUCED RHABDOMYOSARCOMA IN MICE. (E.) Segall, A. (Kupat Holim Ctr., Tel Aviv, Israel), B. Bertini, B. Wechsler and H. Menahem. *Cancer Cytol* 13(1), 1973.
- See also:
- * (Rev): 1801, 1826
 - * (Chem): 1874, 1969
 - * (Viral): 2042, 2045, 2049, 2050, 2051, 2053, 2059, 2064, 2070, 2080, 2084, 2107

- 2246 THE DISTRIBUTION OF GASTRITIS IN CARCINOMA OF THE STOMACH. (E.) Du Plessis, D. J. (Dept. Surg., U. Witwatersrand, Johannesburg, South Africa). *Br J Surg* 61(7):521-523, 1974.

Twenty-one stomachs resected for carcinoma, two stomachs resected for lymphomas, and one stomach resected for carcinoma in a person suffering from pernicious anemia were studied histologically using the "Swiss-roll" technique. Of the 21 stomachs resected for carcinoma, chronic gastritis was found in relation to the tumor in each case. This was mostly chronic atrophic gastritis, but close to the tumor there was a zone of hyperplasia. The distribution of the chronic gastritis varied and two types were recognized: in 17 instances it extended continuously from the pylorus proximally up to or beyond the carcinoma; and in four stomachs the gastritis occurred only in the vicinity of the tumor and did not extend from the pylorus. The first type could be due to reflux of the duodenal contents into the stomach, while the second type could not be due to duodenal reflux. In the patient with pernicious anemia, the carcinoma was in the fundic gland area of the stomach and the chronic gastritis extended from the pylorus proximally to beyond the carcinoma. The two stomachs resected for lymphosarcomas revealed both types of distribution of chronic gastritis. The data indicate that there may be two kinds of carcinoma: one type is associated with the epithelial hyperplasia of the chronic gastritis, possibly resulting from duodenal reflux into the stomach; and the other is also associated with chronic gastritis but the distribution does not suggest duodenal reflux. The relationship of hyperplastic gastritis to the carcinoma in every instance strongly suggests a causal relationship in the pathogenesis of carcinoma.

- 2247 HEREDITY AND HUMAN CANCER. (E.) Knudson, A. G., Jr. (U. Texas Hlth. Sci. Ctr., Houston). *Am J Pathol* 77(1):77-84, 1974.

The pathogenesis of a variety of dominantly inherited childhood tumors (retinoblastoma, Wilms' tumor, and neuroblastoma) and adult tumors (polyposis of the colon, the basal cell nevus syndrome, and pheochromocytoma, which also occurs in children) can be explained in terms of a model supposing that the tumors occur in two steps, both of which may be mutational. The first step involves the inheritance of an altered germ cell, the second mutation in a somatic cell. The nonhereditary forms of these tumors may also involve two steps, both occurring in somatic cells. In both cases, the second mutation renders the doubly mutated cell defective for some tissue-specific function associated with the regulation of cell proliferation. Evidence indicates that compared with the noninherited form, the dominantly inherited form of various tumors is associated with tumor multiplicity and earlier onset; this is predicted by the proposed model. Recessive genes for cancer susceptibility and environmental carcinogens may interact with each other and with these "cancer genes" to increase the probability that a cancer cell will be formed and, once formed, nurtured to a full-fledged tumor. Any program of cancer prevention should be directed at identifying "cancer

gene" carriers and at reducing environmental mutagens which might increase mutation of these genes, either in germ cells or in somatic cells.

- 2248 ELECTRON MICROSCOPIC STUDY OF FUNCTIONAL AND DYSFUNCTIONAL HUMAN MAMMARY GLANDS. (E.) Ozzello, L. (U. Lausanne Med. Sch., Switzerland). *J Invest Dermatol* 63(1):19-26, 1974.

This review is concerned with the functional significance of ultrastructural finding and the morphologic expression of the presumed early evolutionary phases of mammary carcinomas. The paucity of organelles in the ultrastructure of the normal resting mammary epithelium indicates that secretory activity is carried out only to a limited extent. A band of avascular stroma surrounds the ducts and ductules and is separated from the vascularized stroma by "delimiting fibroblasts." There is reason to believe that the structures lying between the epithelium and the delimiting fibroblasts constitute a morphophysiological unit (epithelial-stromal junction, ESJ) which mediates the transport of the materials to and from the epithelium. The ultrastructural and chemical disruption of this ESJ is likely to affect the evolution of dysplastic lesions. Dysplastic epithelium may appear atrophic and hyperplastic or may resemble the ultrastructure of apocrine epithelium. Hyperplastic epithelium shows prominent organelles which in severe hyperplasias resemble the ultrastructural features of carcinoma cells and support the hypothesis that some hyperplasias lead to neoplastic transformation; definite proof of this hypothesis is lacking. Basically, the ultrastructure of all types of mammary carcinoma cells is characterized by prominent organelles; the frequent variations from cell to cell suggest various functional states of the neoplastic cells. This basic ultrastructure is retained by carcinoma cells cultured *in vitro* even after heterotransplantation in nude athymic mice. The basal laminae of intraepithelial mammary carcinomas have gaps through which neoplastic cells sometimes protrude into the stroma and give rise to foci of beginning invasion. The smallest of these foci are detectable only with the electron microscope.

- 2249 CANCER OF THE PROSTATE AMONG MEN WITH BENIGN PROSTATIC HYPERPLASIA. (E.) Greenwald, P. (New York State Dept. Hlth., Cancer Control Bur., Albany), V. Kirmss, A. K. Polan and V. S. Dick. *J Natl Cancer Inst* 53(2):335-340, 1974.

The occurrence of prostate cancer, the cause of death, and the epidemiologic features of prostatic hyperplasia were studied among 838 patients who had had subtotal prostatectomies for benign prostatic hyperplasia and 802 age-matched controls. All subjects were less than 80 yr old, the average age being 63 yr. Patients were followed for 10.7 yr and controls for 11.2 yr. Prostate cancer developed among 24 of the patients and 26 of the controls. This difference was not significant, the estimated relative risk of developing prostate cancer being 0.88 for both groups. Using the modified life-table method, the prostate hyperplasia patients were fol-

lowed for 8115 person-yr, while the controls were followed for 8290 person-yr. Among the former group, there was no significant correlation between the development of prostate cancer and the weight of the hyperplastic gland originally removed. The incidence of bladder cancer did not differ between patients and controls. The patients and controls did not differ significantly in terms of marital status, race, occupation, or place of birth or death. Coffee was used slightly, but not significantly, more frequently by the patients than by the controls; the two groups did not differ in terms of diabetes, drug-use history, family medical history, or smoking or drinking habits. It is concluded that statistical analysis for interactions between prostatic hyperplasia and prostatic cancer revealed no association between the two diseases.

- 2250 RELATION BETWEEN BENIGN PROSTATIC HYPERPLASIA AND CANCER OF THE PROSTATE: A PROSPECTIVE AND RETROSPECTIVE STUDY. (E.) Armenian, H. K. (Johns Hopkins U. Sch. Hygiene Pub. Hlth., Baltimore, Md.), E. L. Diamond, A. M. Lilienfeld and I. D. J. Bross. *Lancet* 7873:115-117, 1974.

Prospective and retrospective epidemiological studies were conducted to investigate the relationship between benign prostatic hyperplasia (BPH) and prostatic cancer. In the prospective study, 296 BPH cases and 229 age-matched controls were traced from 1945 or 1965 until death or the end of 1972. The age-adjusted death-rate from prostate cancer was 3.7 times higher in the BPH than the control group. For the retrospective study, hospital records of 290 prostate cancer cases and 290 age-matched controls were compared. Matched-pair analysis of the antecedent hospital admission records revealed a relative risk of 5.1 for prostate cancer in patients seen earlier for benign prostatic enlargement. These findings suggest the need for a randomized controlled clinical study of prostatectomy as a preventive measure for prostatic cancer in symptom-free BPH patients who have additional epidemiological characteristics associated with a high risk of prostate cancer. A more definitive evaluation of the relation between BPH and prostate cancer could possibly yield a potential for prevention.

- 2251 DIFFERENTIAL DIAGNOSIS OF PRESTAGE AND EARLY STAGE CARCINOMA OF THE CERVIX BY PROSPECTIVE CYTOLOGY. (E.) Breinl, H. (No affiliation). *Cancer Cytol* 13(1), 1973.

- 2252 CERVICAL DYSPLASIAS. THE COLPO-CYTOHISTOLOGICAL RELATIONSHIPS (CORRELATIONS). (E.) Burculeț, V. (Oncol. Inst., Bucharest, Romania), N. Boguleanu and R. Dutu. *Cancer Cytol* 13(1), 1973.

- 2253 THE PATHOGENESIS OF A MURINE OVARIAN CARCINOMA AND TREATMENT WITH HETEROLOGOUS ANTISERUM. (E.) Knapp, R. C. (Harvard Med. Sch., Boston, Mass.) and S. E. Order. *Cancer Cytol* 13(1), 1973.

- 2254 EARLY DIAGNOSIS OF MALIGNANT POLYPS. (E.) Sanchez de Calvosa, L. E. (No affiliation). *Cancer Cytol* 13(1), 1973.

- 2255 THE SIGNIFICANCE AND ROLE OF INTESTINAL METAPLASIA IN GASTRIC PATHOLOGY IN CONNECTION WITH THE EARLY DIAGNOSIS OF NEOPLASMS. (E.) Cernat, M. J. ("Dr. V. Babes" Inst. Pathol., Med. Genetics, Bucharest, Romania) and S. Gabriela. *Cancer Cytol* 13(1), 1973.

- 2256 HISTOGENESIS OF OAT CELL CARCINOMA OF THE BRONCHUS. (E.) Hachmeister, U. (Dept. Pathol., U. Giessen, Germany). *Cancer Cytol* 13(1), 1973.

- 2257 THE NATURE OF KINETICS OF PRECANCEROUS DYSPLASIA AND CARCINOMA *IN SITU* "CONVERTERS". (E.) Kwoczyński, M. Z. (Med. Sch., Wrocław, Poland). *Cancer Cytol* 13(1), 1973.

- 2258 STUDIES ON THE HISTOGENESIS OF INVASIVE CARCINOMA OF THE UTERINE CERVIX. (E.) Rubio, C. A. (Karolinska Inst., Stockholm, Sweden) and B. Lagerlof. *Cancer Cytol* 13(1), 1973.

- 2259 ELECTRON MICROSCOPIC AND MORPHOMETRIC ANALYSIS OF PRECANCEROUS DYSPLASIA. (E.) Stegner, H. E. (U. Hosp., Eppendorf, Germany). *Cancer Cytol* 13(1), 1973.

- 2260 THE MORPHOLOGY OF THE DEVELOPMENT OF THE INTRAEPITHELIAL CARCINOMA COLLI UTERI. (E.) Stucin, M. (Gynecol. Clin., Ljubljana, Yugoslavia). *Cancer Cytol* 13(1), 1973.

- 2261 THE METAPLASTIC PROCESS IN THE CERVIX UTERI. DEFINITION, COLPOSCOPIC, CYTOLOGIC, HISTOPATHOLOGIC ASPECTS. SOME IDEAS IN CONNECTION WITH THIS PROCESS. (E.) Ungureanu, M. (Oncol. Inst., Bucharest, Romania), M. Cringu and I. Mindru. *Cancer Cytol* 13(1), 1973.

See also:

- * (Rev): 1811
* (Chem): 1887, 1956, 1982, 1996

- 2262 CANCER MORBIDITY AMONG TWO MALE COHORTS WITH INCREASED ALCOHOL CONSUMPTION IN FINLAND. (E.) Hakulinen, T. (Finnish Cancer Registry, Helsinki), L. Lehtimäki, M. Lehtonen and L. Teppo. *J Natl Cancer Inst* 52(6):1711-1714, 1974.

The correlation between alcohol consumption and morbidity from cancer was investigated in two male Finnish populations. For the first population, the files of the Finnish Cancer Registry on cancer of the esophagus, liver, and colon (1965-1969) and lung (1968) in males were checked against the files of the "alcohol abuser" registry, a group totaling about 205,000 males. Excess morbidity was observed from cancer of the esophagus, liver, and lung but not from cancer of the colon. For the second population, the files on a group of chronic skid row alcoholics, numbering about 4370 annually in 1967-1970, were checked against those of the Finnish Cancer Registry (1967-1970). Excess morbidity was observed from cancer of the pharynx, esophagus, and lung; excess total cancer morbidity was also noted. The results agree with the hypothesis of a correlation between alcohol consumption and morbidity from cancer of the pharynx, esophagus, and liver. The high incidence of lung cancer in both populations may be attributed to concomitant heavy smoking, which may also be partly responsible for the excess morbidity from esophageal cancer.

- 2263 STUDY FINDS CANCER-WOODWORKING TIE. (E.) Anonymous. *Eng News Record* 195(15):15, 1974.

Results of a retrospective study conducted by the Washington State Dept. of Social and Health Services and released by the National Institute for Occupational Safety and Health have shown an increased evidence of cancer deaths among union workers in wood-related occupations. Results based on union worker death records showed that 22.1% of all recent union deaths were due to cancer compared with 17.1% for all U.S. White males over 20 yr of age. The union incidence of cancer-related deaths for ages 55-59 was 28.4% compared with 21.4% in general. The study found excessive death rates over expected for the following: 1) lung cancer in acoustical tile applicators and insulators, probably related to asbestos exposure; 2) colonic, gastric and pancreatic cancers in pile drivers; 3) leukemia-lymphoma in millwrights, millmen, cabinet workers, and lumber and sawmill workers; and 4) lung and gastric cancer in construction workers in major urban areas with a high incidence of colon and urinary tract cancer in New York City workers.

- 2264 CERVICAL CANCER IN YUGOSLAVIA. II. EPIDEMIOLOGIC FACTORS OF POSSIBLE ETIOLOGICAL SIGNIFICANCE. (E.) Kessler, I. I. (Johns Hopkins U. Sch. Hyg. Public Hlth., Baltimore, Md.), Z. Kulcar, A. Zimolo, M. Grgurevic, M. Strnad and B. J. Goodwin. *J Natl Cancer Inst* 53(1):51-60, 1974.

Epidemiologic factors of etiologic significance were sought in a case-control study of cervical cancer among Moslems and non-Moslems in Yugoslavia. Women

who developed cervical cancer were more likely to manifest behavioral characteristics such as smoking, drinking of alcohol, and diminished religiosity. The cases were significantly shorter, lighter, and less endomorphic than controls similar in age, marital status, religion, and urban/rural residence. They also had somewhat higher systolic and diastolic blood pressures at two different readings. Multiple marriages and early initiation of coitus were more common among the cases. However, coital frequency was consistently lower among Moslem and non-Moslem cases than controls, both at the onset of coital practice and later. Absences from home and extramarital sexual experiences were significantly more common among the first husbands of the cases. An unexpected finding was the twofold or threefold greater mortality, especially at young ages, of first husbands of cases as compared with those of controls. The cases tended to experience more frequent and longer widowhoods beginning at earlier ages than controls. For most of the variables studied, case-control differences among the Moslem women closely resembled those among the non-Moslems. The results of this investigation are consistent with the venereal hypothesis of cervical carcinogenesis, but suggest the need for further investigations of the role of steroid hormones in this disease.

- 2265 EPIDEMIOLOGICAL STUDIES RELATING GENITAL HERPETIC INFECTION TO CERVICAL CARCINOMA. (E.) Nahmias, A. J. (Emory U. Sch. Med., Atlanta, Ga.), Z. M. Naib and W. E. Josey. *Cancer Res* 34(5):1111-1117, 1974.

A large number of epidemiological studies, with a variety of different approaches, have focused in the past decade on the relation of genital herpetic or herpes simplex virus type 2 (HSV-2) infection to cervical cancer. The results reported here of the high frequency of HSV-2 antibodies in young women (≤ 21 years) with cervical carcinoma *in situ* and in women with dysplasia or carcinoma *in situ*, matched for various sexual attributes to control women, provide support for a causal relation. Nevertheless, the various laboratory, histopathological, and statistical problems associated with all epidemiological studies conducted to date do not yet permit a firm conclusion to be reached as to the etiologic role of the genital virus in cervical carcinogenesis.

- 2266 HUMAN CANCER MORTALITY IN RELATION TO POULTRY POPULATION, BY COUNTY, IN 10 SOUTHEASTERN STATES. (E.) Priester, W. A. (Natl. Cancer Inst., Bethesda, Md.) and T. J. Mason. *J Natl Cancer Inst* 53(1):45-49, 1974.

The possible relationship between human cancer deaths and exposure to poultry was studied in 1019 U.S. counties for 1950-69. Deaths from uterine, cervical and ovarian cancers and from multiple myeloma were excessive in high poultry population areas; the significance for the latter two cancers disappeared when data from the high poultry population areas were compared with data from the total United States. The excess of uterine cervical cancer was

probably due to previously defined social determinants rather than to exposure to poultry. The study did not detect any excess risk of lymphomas, Hodgkin's disease, and leukemia in people occupationally exposed to poultry.

- 2267 LEADS IN OESOPHAGEAL CANCER. (E.) Anonymous. *Lancet* (7879):504, 1974.

A high incidence of esophageal cancer has been found in trans-Saharan, South, and East Africa, in the Caribbean Islands; and in a belt from the Middle East to Northern China. A number of environmental factors have come under suspicion, including heavy metals, alcohol, alcohol contaminants, iron deficiency, tobacco, alkalis, hot drinks, viruses, and nitrosamines. In Africa, an association between maize cultivation and esophageal cancer has been suggested. Pure alcohol has apparently been excluded experimentally as an etiologic factor. It has been suggested that dimethylnitrosamine may be formed during the fermentation of beverages by wild yeasts. Recent experimental and epidemiologic work has suggested a possible role for molds in esophageal carcinogenesis.

- 2268 GASTRIC CARCINOMA IN UGANDA. (E.) Bijlsma, F. (Dept. Pathol., Makerere U., Kampala, Uganda). *Trop Geogr Med* 26(1):1-8, 1974.

A survey over a ten yr period (1961-1970) was made of 370 centrally registered cases of stomach carcinoma in Uganda, including 345 histologically proven and 25 clinically probable cases. They constitute 2.3% of all malignancies registered during this period. Apart from a relatively high proportion of females no uncommon findings regarding site and histology of the tumor and age and sex of the patients were noted. Tribal distribution of the patients reveals a marked preference for Southern and South-Western Ugandan tribes, the latter probably continuous with a previously reported high incidence area of N.W. Tanzania-Rwanda-Burundi. The findings are compared with data about the incidence of the disease in Africans elsewhere in and outside Africa and in East Africa in particular, where curious unexplained differences in local frequency occur.

- 2269 SMOKING, DRINKING AND OESOPHAGEAL CANCER IN AFRICAN MALES OF JOHANNESBURG, SOUTH AFRICA. (E.) Bradshaw, E. (South African Inst. Med. Res., Johannesburg) and M. Schonland. *Br J Cancer* 30(2):157-163, 1974.

A study of the smoking and drinking habits of 196 esophageal cancer cases and 1064 control patients was made. All subjects were African males aged 35 yr or more, drawn from a mainly urbanized population. It was found that tobacco smoking was prevalent and that pipe tobacco (used in pipes or in hand rolled cigarettes) was used more frequently than has been found in westernized countries. The drinking of alcohol was also a prevalent habit.

Tribal affiliations were examined and all three of these factors showed differences between cases and controls. Further analysis of smoking and drinking together showed that only smoking had a positive association with esophageal cancer, and this was also true after tribal adjustment had been made. A comparable analysis of data on Durban African males yielded similar findings. It is concluded that tobacco smoking was a powerful esophageal insult but it was not shown that alcohol was important in the development of esophageal cancer. Cigarette tobacco does not appear to be a significant esophageal insult but pipe tobacco does, and the use of both these types of tobacco together may have a synergistic effect. Tribal affiliation has bearing on the smoking pattern.

- 2270 HODGKIN'S DISEASE CLUSTERING IN FAMILIES AND COMMUNITIES. (E.) Dworsky, R. L. (U. Southern California, Sch. Med., Los Angeles) and B. E. Henderson. *Cancer Res* 34(5):1161-1163, 1974.

A case-controlled study of Hodgkin's disease was conducted in the early 1970's. An unusual clustering of Hodgkin's disease was found in three groups: a married couple; seven heroin addicts; and five graduates of a particular junior high school. In the first group, the husband was diagnosed as having Hodgkin's disease in 1948, after having been married for 5 yr. In 1965, the wife was found to have the disease. The heroin addicts, all of whom administered the drug i.v. in groups and six of whom lived within 1 square mile of each other, ranged in age from 21-43 yr and represent two histologic types, nodular sclerosis and mixed cellularity. In the third group, one teacher and five graduates of a junior high school developed Hodgkin's disease between 1967 and 1971; all came into direct or indirect contact with one or more of the others. These clusters suggest the possibility of an environmental factor in Hodgkin's disease, such as a horizontally transmitted agent as one factor in the pathogenesis of the disease.

- 2271 CARCINOMA OF HARD PALATE IN INDIA IN RELATION TO REVERSE SMOKING OF CHUTTAS. (E.) Reddy, C. R. R. M. (Andhra Med. Coll., Visakhapatnam, S. India). *J Natl Cancer Inst* 53(3):615-619, 1974.

Hindu women in Visakhapatnam, South India, have twice the incidence of hard-palate carcinoma as do men. Of 600 oral and oropharyngeal carcinomas diagnosed at the King George Hospital in Visakhapatnam between September 1970 and October 1973, nearly half occurred among females. The mean age of the female patients with carcinoma of the hard palate (73.8% of the female patients) was significantly greater than that of the males with carcinoma of the hard palate. Reverse smoking of chuttas predominated among the patients with carcinomas, whereas all other smoking habits predominated among the controls. Most of the carcinoma patients either chewed tobacco or smoked, while many of the controls did neither. The patients and controls did not differ significantly in terms of pan

and betel nut chewing, consumption of alcohol, dental hygiene, or religion. For the females, the estimated risk of developing hard-palate carcinoma was 132 times greater among those who indulged in reverse smoking of chuttas than among those without the habit. The risk of developing cancer of the buccal mucosa was not greater among reverse smokers. Compared to the males, the females had less exophytic growths and perforations but more plaquelike ulcers and verrucous growths. Grade II epidermoid tumors were more common among males, with grade I tumors being more common among females. For neither sex was the ordinary smoking of chuttas related to an increased risk of developing carcinomas.

- 2272 CANCER OF THE UPPER ALIMENTARY TRACT AND LARYNX IN POLAND AND IN POLISH-BORN AMERICANS. (E.) Staszewski, J. (Inst. Oncol., Gliwice, Poland). *Br J Cancer* 29(5):389-399, 1974.

Age-specific mortality rates for cancers of the buccal cavity, pharynx, esophagus, and larynx were computed for Poles between the years 1959 and 1972 and for Polish-born Americans in the periods 1950 and 1959-1961. The patterns of occurrence of these cancers in Poland appear to be similar to those of other European and American countries, except perhaps for the rather high and still increasing incidence of laryngeal cancer. Among male Polish migrants, however, mortality for these cancers was distinctly higher than among native Poles or Americans. This contrast, which was largest for esophageal and laryngeal cancer, decreased between 1950 and 1959-61, but only among those aged below 65 years. The observed large shifts in the migrant's cancer risk suggest the operation of environmental rather than genetic factors. These shifts are similar to those seen in the incidence of lung cancer among Polish migrants to the U.S.

- 2273 INCREASED MORTALITY DUE TO MALIGNANT TUMORS OF THE LARYNX SINCE 1951 IN THE TOWN OF TURIN AND IN ITALY. (It.) Terracini, B. (Inst. Anat., U. Turin, Italy), G. Pastore and S. Coverlizza. *Tumori* 60(3):221-230, 1974.

An analysis of statistics on age-adjusted mortality for cancer of the larynx in males of all ages in Turin showed an increase from 3.3/100,000 in 1951-1953 to 7.9/100,000 in 1970-1971. The proportion of mortality for cancer of the larynx/mortality for all forms of cancer increased from 2.5% to 4.7% during the same period. Corresponding values for laryngeal cancer mortality in Italy were 3.3/100,000 in 1951-1953 and 5.7/100,000 in 1968-1969. The percentage for cancer mortality of the larynx as related to mortality for all cancer in Italy increased from 2.8 in 1951-1953 to 3.7% in 1968-1969. A comparison of these figures with statistics for France, a country with a standard of medicine and a society similar to those of Italy, showed no increase during this period and a slight tendency to decrease was noted in the ratio of laryngeal cancer mortality to total cancer mortality. Age-

adjusted mortality for cancer of the larynx among males aged 35-64 yr followed a similar pattern, while no changes were evident in the mortality for cancer of the larynx among women in Turin, Italy, or France. The most commonly cited etiological factors for cancer of the larynx are tobacco smoking, air pollution, and pollution of the working environment. Of these factors, it is most likely that the high mortality from cancer of the larynx in Turin is due to pollution of the working environment. This should be studied in more detail.

- 2274 LUNG CANCERS AT AUTOPSY IN A-BOMB SURVIVORS AND CONTROLS, HIROSHIMA AND NAGASAKI, 1961-1970. I. AUTOPSY FINDINGS AND RELATION TO RADIATION. (E.) Cihak, R. W. (Atomic Bomb Casualty Commission, Hiroshima, Japan), T. Ishimaru, A. Steer and A. Yamada. *Cancer* 33(6):1580-1588, 1974.

Autopsies were performed on 3778 persons dying between 1961 and 1970 who had been part of a fixed sample (LSS) consisting of approximately 100,000 persons who were living in Hiroshima or Nagasaki at the time of the 1950 census. Among the autopsied cases, lung cancer had been the principal disease in 184 and was incidental in an additional 20. The male:female ratio was 0.72:1 for the entire LSS population, 1.07:1 for the autopsy series; and 2:1 for lung cancer. Histologically, 32% of the tumors were epidermoid, 19% were small cell anaplastic, 29% were bronchogenic adenocarcinoma, 9% were bronchiolo-alveolar, and 11% were other types of carcinoma. Epidermoid carcinoma and small cell anaplastic carcinoma were significantly more frequent in males than females, but the incidence of the other histologic types did not differ according to sex. Small cell anaplastic carcinomas were significantly more common in persons exposed to the atomic bomb than in unexposed persons (relative risk 3.9). Epidermoid carcinomas and bronchogenic adenocarcinomas were slightly, but not significantly, more common in irradiated persons. Age at the time of irradiation did not appear to affect the lung cancer rate or histologic type. Metastases to the liver were significantly more frequent among persons exposed to 200 rad or more. There was no significant association between lung cancer and tuberculosis. Nor was there any significant relationship between the presence of bronchial epithelial alterations and the radiation exposure dose. There was a probable association between lung cancer and ionizing radiation exposure independent of smoking habits. No data were available for a study of the possible effect of internal irradiation.

- 2275 DATA FROM ELEVEN UNITED STATES AND CANADIAN COLLEGES OF VETERINARY MEDICINE ON PANCREATIC CARCINOMA IN DOMESTIC ANIMALS. (E.) Priester, W. A. (Natl. Cancer Inst., Bethesda, Md.). *Cancer Res* 34(6):1372-1375, 1974.

To determine characteristics of dogs with pancreatic carcinoma and the relative frequency with which this carcinoma occurs in other common domestic animal species, a case series compiled from medical records

of animal patients was compared with a veterinary clinic-hospital reference population. Pancreatic carcinoma in dogs was slightly more frequent in females, strongly associated with increasing age, and was found excessively only in the Airedale terrier breed. Estimated rates per 100,000 patient yr at risk were: cattle, 3.9; horses, 1.6; dogs, 17.8; and cats, 12.6. Based on anatomical similarities, a bile-reflux hypothesis recently proposed for humans could apply to pancreatic carcinoma in several domestic animal species, but not in all. Two dogs with pancreatic carcinoma and thyroid adenoma may have been analogous to an endocrinopathy reported in an autopsy series of human patients with pancreatic carcinoma. This suggested that the diversity of diet, environment and duct relationships among domestic animals could permit a comparative study of the possible frequent effects of these variables on the pancreas and thus answer questions about their role in pancreatic carcinogenesis.

- 2276 RETINOBLASTOMA IN HUNGARY, 1960-1968. (E.) Czeizel, A. (Natl. Inst. Public Hlth., Budapest, Hungary) and J. Gardonyi. *Humangenetik* 22(2):153-158, 1974.

Of the children born in Hungary between 1960 and 1968, 43 were found to suffer from confirmed retinoblastoma, indicating that 1 in 30,000 live births may develop retinoblastoma. This relatively low frequency may be attributed, among other things, to a lower paternal age than in other countries. Other possible explanations for this low rate could be attributed to the inapparent effect of medical contraselection or that not all cases of retinoblastoma were diagnosed clinically or histologically and the resultant failure to report the cases. Of the 43 cases detected, 69.8% were unilateral retinoblastomas and 78% were alive at the time of the survey in 1971. The sex ratio showed no significant deviation from the normal value. The mutation rate, estimated by the so-called direct method, was 6×10^{-6} .

- 2277 A MORPHOMETRIC STUDY OF PULMONARY CANCER. (E.) Gerstl, B. (VA Hosp., Palo Alto, Calif.), P. Switzer and R. Yesner. *Cancer Res* 34(1):248-254, 1974.

A morphometric procedure yielding dependable quantitative data on structural components of pulmonary carcinomas was devised. Semiquantitative data on necrobiosis, karyorrhexis, and infiltrating inflammatory cells were also obtained. Sections of tumor cut in three mutually perpendicular directions revealed minor quantitative intratumor variation for small-cell and epidermoid carcinoma but greater ones for adenocarcinoma. Small-cell carcinomas revealed little variation in the amount of tumor and stroma while stroma amounted to up to 50% of total areas in epidermoid carcinoma. Small-cell carcinoma showed better vascularization than the other three types of tumors. It was nearly devoid of lymphocytes, plasma cells, and macrophages. A case of a long-term survivor did not differ in this respect from the others. Macrophages were found only in

epidermoid carcinoma. Amount of necrobiosis and karyorrhexis did not correspond to that of necrosis. The number of tumor cell nuclei per unit area differed significantly between individual cases of epidermoid and adenocarcinoma but was more uniform in small-cell carcinoma.

- 2278 ASYNCHRONOUS DNA SYNTHESIS AND ASYNCHRONOUS MITOSIS IN MULTINUCLEAR OVARIAN CANCER CELLS. (E.) Sheehy, P. F. (Mem. Sloan-Kettering Cancer Ctr., N.Y., N.Y.), T. Wakonig-Vaartaja, R. Winn and B. D. Clarkson. *Cancer Res* 34(5):991-996, 1974.

The synchrony of DNA synthesis and mitosis in multinuclear cells from two patients with ovarian carcinomatous ascites was studied with autoradiographic techniques. The patients had previously been treated with surgery, radioactive phosphorus (^{32}P), radiotherapy, and chlorambucil. The incidence of binuclear, trinuclear, quadrinuclear, and multinuclear (five or more nuclei/cell) in both tumors was estimated. Asynchronous DNA synthesis and asynchronous mitosis were frequent in the binuclear and trinuclear pools in the first patient and in all the cell pools in the second patient. Cytogenetic studies demonstrated aneuploidy in the tumor cells removed from both patients. The results demonstrate that the nuclei in multinuclear cells from treated ovarian cancer patients are capable of individual DNA synthesis and mitosis and are probably not dependent on cytoplasmic controlling factors.

- 2279 EVALUATION OF CANCER RISK FACTORS IN A RETIREMENT COMMUNITY. (E.) Henderson, B. E. (U. Southern California Sch. Med., Los Angeles), E. Bogdanoff, V. R. Gerkins, J. SooHoo and M. Arthur. *Cancer Res* 34(5):1045-1048, 1974.

A mail questionnaire with 73% return was distributed to residents of a retirement community with median age of 71 as part of a study of factors associated with cancer risk in the elderly. Maternal and paternal age and birth order were not associated with increased risk. With the exception of a positive association between heart disease and prostate cancer, there was no association between a personal or familial history of allergy, diabetes, and heart disease and risk to the cancers studied. There was a familial risk associated with skin, colon, and breast cancer. A study of spouse cancer indicated that the familial risk of skin and colon cancer was related to environmental factors, whereas the risk to breast cancer appeared to be primarily genetic.

- 2280 *IN VITRO* DETERMINATION OF THYMIDINE- ^3H LABELING INDEX IN HUMAN SOLID TUMORS. (E.) Livingston, R. B. (M.D. Anderson Hosp. Tumor Inst., Houston, Texas), U. Ambus, S. L. George, E. J. Freireich and J. S. Hart. *Cancer Res* 34(6):1376-1380, 1974.

A rapid and reproducible method for the preparation of autoradiographs from single-cell suspensions of

human tumor cells, including melanoma and lung carcinoma, is described. Tritiated thymidine of high specific activity (6.0 C/mM) was used so that autoradiographs could be developed and read at 24 hr after the sample was taken. Samples were prepared in duplicate, and a Hypaque-Ficoll density gradient was used to separate viable tumor cells from dead tumor cells, red blood cells, and tissue debris. Autoradiographs were prepared from single-cell suspensions of the viable tumor cells. The labeling index percentage (the number of labeled tumor cells/100 tumor cells counted) was determined from the autoradiograph of each sample fraction. A twofold difference between labeling indices could be declared significant at $p < 0.05$. The values obtained for the labeling indices of a variety of tumors, including melanoma and oat cell carcinoma, were comparable to those reported using other methods, including *in vivo* labeling. The data support previous observations that the labeling index varies little in simultaneous biopsy specimens from the same patient, at least in melanoma. The method described lends itself well to the serial study of the labeling index as a measure of the proliferative fraction of tumors obtained from patients with accessible disease.

2281 RELATIONSHIP BETWEEN POLYPOSIS INTESTINALIS AND MALIGNANT DEGENERATION. (PATHOLOGY AND EPIDEMIOLOGY). (E.) Chiurco, G. A. (CESPRE - U. Rome, Italy). *Cancer Cytol* 13(1), 1973.

2282 THE EFFECT OF UNIVERSAL CYTOLOGY SCREENING ON THE INCIDENCE OF INVASIVE CARCINOMA OF THE CERVIX. (E.) Ragula, B. D. (St. Joseph's Hosp., London, Canada). *Cancer Cytol* 13(1), 1973.

2283 SERO-EPIDEMIOLOGICAL EVIDENCE ASSOCIATING CERVICAL CARCINOMA AND GENITAL HERPES VIRUS INFECTION. (E.) Skinner, G. R. B. (Dept. Virol., U. Birmingham, England). *Cancer Cytol* 13(1), 1973.

2284 SMOKING HABITS AND CANCER IN AUSTRIA. (Ger.) Wrba, H. (Cancer Res. Inst., U. Vienna, Austria). *Cancer Cytol* 13(1), 1973.

2285 THE TEMPORAL AND SPATIAL DISTRIBUTION OF OESOPHAGEAL CANCER AMONG MINeworkERS IN SOUTHERN AFRICA. (E.) Harington, J. S. (Nat'l. Cancer Assoc. South Africa, Johannesburg) and N. D. McGlashan. *Br J Cancer* 28(1):86, 1973.

2286 CHILDHOOD CANCER: AN EPIDEMIOLOGICAL STUDY. (E.) Powell, J. (Queen Elizabeth Med. Ctr., Birmingham, England). *Br J Cancer* 28(1):86-87, 1973.

2287 LUNG CANCER IN MINERS. (E.) Ashley, D. J. B. (Morrison Hosp., Swansea, England). *Br J Cancer* 28(1):87, 1973.

See also:

- * (Rev): 1814, 1817
- * (Chem): 1898, 1999
- * (Phys): 2000
- * (Viral): 2070
- * (Immun): 2150, 2241

- 2288 EFFECTS OF DIALYZABLE TRANSFER FACTOR IN PATIENTS WITH BREAST CANCER. (E.) Oetgen, H. F. (Mem. Sloan-Kettering Cancer Ctr., New York), L. J. Old, J. H. Farrow, F. T. Valentine, H. S. Lawrence and L. Thomas. *Proc Natl Acad Sci USA* 71(6):2319-2323, 1974.

Five patients with advanced breast cancer of the "inflammatory" type were treated with pooled dialyzable transfer factor from leukocytes of healthy adult women. The treatment period ranged from 21-310 days, with the total dose varying from 20-257 ml. The transfer factor did not elicit inflammatory or hypersensitivity reactions nor the formation of antibody to itself; neither did it elicit any hematological or biochemical abnormalities or other side effects. Three patients became responsive (by skin test) to tuberculin and/or streptococcal antigens. Marked partial regression of the breast cancer, lasting 6 months, was observed in one patient. At this point, it is not suggested that pooled transfer factor from healthy donors offers promise in the treatment of patients with breast cancer or any type of cancer.

- 2289 A NEW VARIANT TRANSLOCATION (19q+, 22q-) IN CHRONIC MYELOCYTIC LEUKEMIA. (E.) Gahrton, G. (Inst. Med. Cell Res. Genetics., Karolinska Inst., Stockholm, Sweden), L. Zech and J. Lindstein. *Exp Cell Res* 86(1):214-216, 1974.

Of nine patients with chronic myelocytic leukemia (CML), one, a 40-yr-old woman, exhibited a chromosome abnormality which appeared to be a translocation between the long arms of chromosomes 19 and 22. The patient was positive for the Philadelphia (Ph) chromosome but, in contrast to the other eight CML patients who appeared to have the common translocation between chromosomes 9 and 22, both chromosomes 9 were normal. The same chromosome constitution (i.e., a shorter than normal long arm of chromosome 22 (22q-) (Ph¹) and longer than normal long arm of chromosome 19 (19q+)) was observed in all of 13 metastases examined from this patient. This patient did not appear to differ in clinical pattern or clinical course from other CML patients with the 9q; 22q translocation. The data indicate that the presence of the Ph¹ chromosome is of greater importance in the characterization of the disease than the location of the translocated fragment.

- 2290 GENETIC STUDIES ON FAMILIAL LEUKEMIA. (E.) Kurita, S. (Aichi Cancer Ctr. Hosp., Nagoya, Japan), Y. Kamei and K. Ota. *Cancer* 34(4):1098-1101, 1974.

Familial leukemia in Japan was studied. Among 20 families where familial leukemia occurred in siblings, the parents were first cousins in six (30%), and they were first cousins once removed or second cousins in 2 (10%). Among 200 families where non-familial leukemia occurred, the parents were first cousins in only nine (4.5%), indicating that the incidence of consanguineous marriage is high in fami-

lial leukemia in siblings. The age of the patient at the time of onset of familial leukemia in children of first cousin parents was lower than that of cases whose parents were not related. These findings suggest that genetic factors play an important role in the etiology of familial leukemia occurring in siblings.

- 2291 HUMAN MALIGNANT MELANOMAS OF THE UVEA IN CELL CULTURES. (E.) Vrba, M. (Pediatr. Res. Inst., Brno, Czechoslovakia). *Neoplasma* 21(4):421-432, 1974.

Twenty-five human malignant melanomas were cultivated *in vitro* on a glass surface using an explant method, Epl medium supplemented with calf neonatal serum, and in 10 cases using an artificial network to separate a primary cell culture with fragments and fibroblasts from the primary one growing under the network at the bottom of the culture vessels. Twenty-two melanomas on a glass surface and all melanomas cultivated with the network developed an outgrowth. Cultures were maintained 14-193 days. A long-term culture derived from a mixed type of choroid malignant melanoma was obtained and it has been cultivated for 4 yr. In primary cell cultures, round, bipolar, and multipolar pigmented or unpigmented melanocytes, fibroblasts, and macrophages were observed. The cell cultures growing under the artificial network were more uniform. Bipolar melanocytes with very long processes prevailed. Loss of cell contact inhibition was frequently observed.

- 2292 STUDIES ON TRYPTOPHAN METABOLISM IN PATIENTS WITH LYMPHOMA. (E.) Gailani, S. (Roswell Park Memorial Inst., Buffalo, N.Y.), E. Ezdinli, A. Nussbaum, P. Silvernail and E. G. Elias. *Cancer Res* 34(7):1664-1667, 1974.

The 24-hr urinary excretion of certain metabolites of tryptophan was measured in 22 patients with Hodgkin's disease and 18 patients with lymphosarcoma, following the p.o. administration of 2 g L-tryptophan. An assay of hepatic tryptophan pyrrolase activity was done on 15 patients with Hodgkin's disease and 15 patients with lymphosarcoma, and an assay of hepatic kynureninase was done on 11 and 7 patients with Hodgkin's disease and lymphosarcoma, resp. There was increased urinary excretion of kynurenine in 9, of 3-hydroxykynurenine in 16, of kynurenic acid in 4, of xanthurenic acid in 4, and of acetylkynurenine in 3 patients with Hodgkin's disease. There was an increase in urinary excretion of kynurenine in 5, 3-hydroxykynurenine in 7, kynurenic acid in 1, xanthurenic acid in 1, and acetylkynurenine in 5 patients with lymphosarcoma. The increased urinary tryptophan metabolite excretion was more common and more marked in patients with Stage III and IV Hodgkin's disease. This correlation could not be made in the patients with lymphosarcoma because of the limited number of patients with Stage I and II disease. There was no correlation between tryptophan pyrrolase activity and either the level of urinary excretion of tryptophan metabolites or the stage of

the disease. On the other hand, patients with low hepatic kynureninase activity tended to excrete increased quantities of these tryptophan metabolites. Depressed kynureninase activity and increased excretion of tryptophan metabolites were more marked in advanced Stage III and IV Hodgkin's disease.

- 2293 *IN VIVO* HYBRIDISATION OF HUMAN TUMOUR AND NORMAL HAMSTER CELLS. (E.) Goldenberg, D. M. (U. Kentucky Med. Ctr., Lexington), R. A. Pavia and M. C. Tsao. *Nature* 250(5468):649-651, 1974.

A portion of an astrocytic glioma from the brain of a 44-yr-old woman was injected as a fine cell suspension into the cheek pouches of nine male golden hamsters. A large tumor developed in the cheek pouch of only one hamster which died 4 wk later with widespread metastasis. Both *in vivo* and *in vitro*, a continuously propagable tumor cell line was established and termed GB-749. All of the aneuploid tumor cells examined contained both hamster- and human-like chromosomes. The results of karyological investigations indicate that pronounced chromosomal segregation occurs following hybrid formation, where the human chromosomes are preferentially lost. It is suggested that similar mechanisms may be implicated in human cancer, particularly when such fusing agents as parainfluenza viruses are prevalent in man. In the autochthonous tumor-bearing host, fusions of neoplastic with normal cells might provide the tumor with a means for reducing any tumor-specific antigenicity and thereby allow it to escape immunological surveillance mechanisms.

- 2294 CARCINOMATOUS NEUROMYOPATHY: I. ELECTROPHYSIOLOGICAL STUDIES. AN ELECTROPHYSIOLOGICAL AND IMMUNOLOGICAL STUDY OF PATIENTS WITH CARCINOMA OF THE LUNG. (E.) Campbell, M. J. (Newcastle Gen. Hosp., New Castle upon Tyne, England) and D. W. Paty. *J Neurol Neurosurg Psychiatry* 37(2):131-141, 1974.

Quantitative electrophysiological studies were performed on 30 patients with lung cancer but as yet no neurological complications; on 11 patients with known cancer and symptomatic neuromuscular disease; and on 13 age-matched patients with chronic nonspecific neuropathy. Clinical examination revealed proximal limb weakness in 53% of the patients in the lung cancer group and depressed tendon reflexes in 10. The incidence of electromyographic abnormalities was high in the lung cancer patients, confirming the presence of subclinical neuromuscular disease. Small amplitude short duration motor unit potentials, some polyphasic, were evident in 53% of the patients. This change was most severe in the proximal muscles. The electrophysiological and clinical findings correlated with the degree of weight loss and muscle wasting, and also with the advanced state of the neoplastic disease. No close correlation between the neuromuscular disorder and the tumor cell could be made. It was concluded that neuromyopathic syndrome is associated with unusual and characteristic electromyographic findings of prominent myopathic abnormalities in proximal muscles together with scat-

tered spontaneous activity, especially fasciculations. Loss of motor and sensory nerve fibers is common, but nerve conduction is usually normal or only mildly delayed except in later stages. Evidence suggests that the pathological basis of the neuromyopathy is a neuronal and axonal disorder, and that segmental demyelination is uncommon and likely to be an end-stage secondary phenomenon in most cases.

- 2295 A COMPARISON OF THREE *IN VIVO* ASSAYS FOR CELL TUMORIGENICITY. (E.) Petricciani, J. C. (Div. Pathol., Food Drug Administration, Rockville, Md.), R. E. Wallace and D. W. McCoy. *Cancer Res* 34(1):105-108, 1974.

The cortisonized adult hamster, the antithymocyte-treated newborn hamster, and the antithymocyte globulin-treated monkey were compared as *in vivo* test systems for the tumorigenic potential of cells. The newborn hamster and monkey systems were more consistent in allowing the expression of tumors than was the cortisonized hamster when each of four human tumor cell lines was assayed. These cell lines were derived, resp., from epidermoid carcinoma, laryngeal carcinoma, colon adenocarcinoma, and lung fibroblasts transformed with simian virus 40. Cells derived from normal tissues failed to show evidence of tumorigenicity in any of the three animal systems.

- 2296 ULTRASTRUCTURAL DEMONSTRATION OF NUCLEAR BODIES IN PRIMARY OVARIAN CANCER. (E.) Blaustein, A. (New York U. Sch. Med., N.Y.), L. Schenker and M. Saluja. *Gynecol Oncol* 2(1):101-108, 1974.

Nuclear bodies occurring in three cases of serous cystadenocarcinoma and one mesonephroma of the ovary were examined by light and electron microscopy. Numerous nuclear bodies, mostly of type I (about 5 μ m in diameter; homogeneous and agranular or composed of fibrillar material surrounded by a clear halo of variable electron density), were seen in all three cases of serous cystadenocarcinoma. Two of these tumors had type II nuclear bodies (about 0.8 μ m in diameter and composed of concentrically arranged fibrils; surrounded by a clear halo), and one had type III bodies (0.5 μ m in diameter with a microfibrillar cortex surrounding osmiophilic granules and separated from the nucleoplasm by a clear halo). One type IV nuclear body (0.4 μ m in diameter with a microfibrillar cortex and a large central osmiophilic mass) was observed. The nuclear bodies seen in the mesonephroma were large intranuclear vacuoles, partially membrane bound, containing large osmiophilic, eccentric, oval-shaped structures which contained granules of varying density; attached to the outer membrane was a small satellite body of similar structure. Most nuclei showed a predominance of euchromatin, and nuclear bodies were more frequent in cells with multiple or large nucleoli. The nuclear bodies observed in these tumors resembled those found in other tumors, other sites, and other disease processes. They do not appear to result from lysosomal digestion. They may represent protein synthesis for which the corresponding enzyme is either inactivated or not synthesized.

- 2297 HUMAN SERUM ALBUMIN PHENOTYPE ACTIVATION IN MOUSE HEPATOMA-HUMAN LEUKOCYTE CELL HYBRIDS. (E.) Darlington, G. J. (Kline Biol. Tower, Yale U., New Haven, Conn.), H. P. Bernhard and F. H. Ruddle. *Science* 185(4154):859-862, 1974.

Murine hepatoma cells that secreted mouse serum albumin were fused with human leukocytes that did not produce albumin. The resulting hybrids secreted both mouse and human serum albumin, as demonstrated by immunoelectrophoretic techniques. The activation of the human genome suggests that the mapping of genes governing specialized functions in somatic cell hybrids may be accomplished by using nondifferentiated human cells as a parental line. These studies also suggest the importance of genome dosage in phenotype activation, since in all instances activation was observed in hybrids that possessed two genomes from the differentiated parent to one from the nondifferentiated parent. Expression of human serum albumin is consistent with the hypothesis that the murine genome contributes activators to those hybrids retaining the albumin structural gene.

- 2298 CONTROL OF 3T3 CELL PROLIFERATION BY CALCIUM. (E.) Boynton, A. L. (Div. Biol. Sci., Natl. Res. Council Canada, Ottawa), J. F. Whitfield, R. J. Isaacs and H. J. Morton. *In Vitro* 10(1-2):12-17, 1974.

When a population of 3T3 mouse cells was subcultured regularly at confluency, the original epithelioid or stellate cells disappeared and, by the ninth passage, had been replaced by spindle-shaped cells. The original cells proliferated only when the extracellular calcium concentration exceeded 0.1 mM, and their proliferative activity became maximum only when the calcium concentration was 0.5 mM. The spindle-shaped cells were much more sensitive to proliferative stimulation by calcium. Although these cells also could not proliferate without extracellular ionic calcium, they proliferated maximally in the presence of as little as 0.05 mM calcium. Thus, calcium is a major regulator of the proliferation of 3T3 mouse cells. Moreover, it appears that the sensitivity of the proliferative machinery to the calcium ion can vary greatly within an established cell line.

- 2299 UNMASKING OF NERVE GROWTH FACTOR MEMBRANE-SPECIFIC BINDING SITES IN SYNCHRONIZED MURINE C 1300 NEUROBLASTOMA CELLS. (E.) Revoltella, R. (Lab. Cell Biol., CNR, Rome, Italy), L. Bertolini and M. Pediconi. *Exp Cell Res* 85(1):89-94, 1974.

Murine C 1300 neuroblastoma cells, maintained *in vitro* in continuous cell suspension, are able to specifically bind onto their membrane surface the Nerve Growth Factor (NGF), a protein which controls the growth of sympathetic cells during development and throughout adult life. Murine C 1300 neuroblastoma cells were synchronized in interphase (G1) then resuspended in complete medium and plated. Every 2 hr over the next 32 hr, they were studied to determine the rate of DNA synthesis, the rate of total protein synthesis, the cell mitotic index, the total cell count/

single culture and their viability, and the change in the cell specific binding capacity for NGF. During the late G1 and early S phase of the cell cycle, the neuroblastoma cells unmasked on their membrane surfaces specific binding sites for NGF. During these phases, the cells firmly bound specifically with the NGF covalently coated onto the surfaces of sheep blood erythrocytes, leading to the formation of 'rosettes'. The binding reaction proceeded at 2 C within 10 min and was not modified by the presence of the medium of 0.02% N-azide or 0.01 M EDTA. Rosette formation was prevented by mild trypsin treatment of the cells, although the binding reaction reappeared within 2 hr.

- 2300 PREVENTION OF MALIGNANT CHANGE IN MAMMALIAN CELLS DURING PROLONGED CULTURE *IN VITRO*. (E.) Goldblatt, H. (Louis D. Beaumont Mem. Res. Labs., Mt. Sinai Hosp., Cleveland, Ohio) and L. Friedman. *Proc Natl Acad Sci USA* 71(5):1780-1782, 1974.

Primary cell cultures were developed from a mixture of epithelial cells and fibroblasts obtained *via* the trypsinization of primarily epidermal skin fragments from 18-day rat embryos of the Sprague-Dawley-derived Holtzman strain. These cultures were grown in tightly rubber-stoppered T-60 glass flasks kept at 37 C. After 13 months, the subcultures of the 52nd passage yielded the first tumor, which proved transplantable to young female Holtzman rats. A second group of subcultures, derived from the 22nd passage of the original culture, were grown under the same conditions but with the addition of 1% oxyhemoglobin; they failed to yield a tumor within 23 months of repeated subculture. A return of these cultures to the regular medium, without hemoglobin, yielded a tumor in 4 months, after 12 passages. Cultures of transformed cells which had regularly yielded a transplantable tumor for 6 yr (up to the 305th passage) continued to yield transplantable tumors when 1% oxyhemoglobin was added to the medium. The cells remained highly atypical microscopically, and there was no indication of reversal of the malignancy. Although oxyhemoglobin in the medium of cell cultures seems to have had the ability to prevent the development of malignancy, it did not reverse established malignant transformation of the cells.

- 2301 DIFFERENT CYCLIC CHANGES IN THE SURFACE MEMBRANE OF NORMAL AND MALIGNANT TRANSFORMED CELLS. (E.) Shoham, J. (Dept. Genetics., Weizmann Inst. Sci., Rehovot, Israel) and L. Sachs. *Exp Cell Res* 85(1):8-14, 1974.

Golden hamster embryo fibroblasts transformed by Rous sarcoma virus or dimethylnitrosamine and 3T3 mouse fibroblasts transformed by simian virus 40 (SV40) or SV40 + polyoma virus were agglutinated by Concanavalin A (Con A) and wheat germ agglutinin in interphase, as were normal fibroblasts in mitosis. In contrast, normal fibroblasts in interphase and transformed fibroblasts in mitosis were not agglutinated by these lectins. The percentage of fluorescent cells at nonsaturation concentrations of fluorescent Con A was also higher with transformed interphase

and normal mitotic cells than with normal interphase and transformed mitotic cells. Under the same conditions, a similar number of radioactively labeled Con A molecules were bound to normal and transformed cells in interphase and mitosis. These results indicate different cyclic changes in the surface membranes of normal and transformed fibroblasts. Thus in their interaction with these lectins, normal mitotic cells resemble transformed interphase cells and transformed mitotic cells resemble normal interphase cells. The data suggest that there is a reversed cyclic change in the mobility of specific surface membrane sites in normal and transformed cells.

2302 THE SURFACE PROPERTIES OF SOME HUMAN INTRACRANIAL TUMOUR CELL LINES IN RELATION TO THEIR MALIGNANCY. (E.) Sherbet, G. V. (U. Coll. Hosp. Med. Sch., London, England) and M. S. Lakshmi. *Oncology* 29(4):335-347, 1974.

The electronegativity of the surfaces of eight human astrocytoma lines, three lines of meningioma, and one line of normal fetal brain cells was investigated with the isoelectric equilibrium method. No changes in the surface isoelectric points (pI) of the cell lines occurred in relation to the time the cells had been maintained in culture. The pIs of the astrocytoma cell lines correlated extremely well with the malignancy of the tumors. The fetal brain cells showed the lowest pI and in increasing order of pI were followed by the highly malignant grade III and IV astrocytomas and the less malignant grade I and II astrocytomas. Meningiomas possessed an intermediate pI value. The experiments have also indicated that the more malignant astrocytomas possess surface coat material which appears to be susceptible to trypsinization; such material was not found on the other cells tested. It is suggested that this trypsin-labile surface coat material on the grade III and IV tumors may be associated with their malignancy.

2303 TUMOR CELL-SURFACE ORGANIZATION: DIFFERENCES BETWEEN TWO TA3 SUBLINES. (E.) Friberg, S. (Karolinska Inst. Med. Sch., Stockholm, Sweden), J. Molnar and G. I. Pardoe. *J Natl Cancer Inst* 52(1):85-93, 1974.

Two ascites-converted sublines, TA3-Ha and TA3-St, from a strain A mouse mammary adenocarcinoma, TA3, were studied. Line TA3-St does not grow in allogeneic mouse strains; line TA3-Ha proliferates in all strains. The membrane characteristics of the two tumors were compared using five heterophil agglutinins with known carbohydrate specificities. TA3-Ha cells were not agglutinated by Concanavalin A (Con-A), or agglutinins from *Phaseolus vulgaris* (PHA) or *Bandeiraea simplicifolia* (Bs) whereas TA3-St cells were. By contrast, agglutinins from *Helix pomatia* (Hp) agglutinated TA3-Ha but not TA3-St cells. *Triticum vulgaris* agglutinins agglutinated both lines. Using ¹²⁵I-labeled preparations of Con-A or PHA the same number of binding sites were found for each agglutinin in both lines. TA3-Ha cells sensitized with Con-A bound more PHA than untreated cells. The results also show that Con-A and PHA bind to in-

dependent cell-surface receptors. Con-A or PHA agglutinated TA3-Ha cells treated with proteases but not cells treated with neuraminidase. The results suggest differences in carbohydrate-containing macromolecules on the cell surface of the two TA3 sublines, some of which are in "crypts" on the surface of the immunoresistant TA3-Ha cells.

2304 EFFECT OF PROTEOLYTIC INHIBITORS ON GROWTH AND SURFACE ARCHITECTURE OF NORMAL AND TRANSFORMED CELLS. (E.) Collard, J. G. (Netherlands Cancer Inst., Amsterdam) and L. A. Smets. *Exp Cell Res* 86(1):75-80, 1974.

Protease inhibitors were tested for their effect on the growth of normal and simian virus 40 (SV40)-transformed mouse fibroblasts. The protease inhibitors *p*-tosyl-L-arginine methyl ester HCl and egg-white trypsin inhibitor, which act competitively on proteases, reduced the growth of transformed cells more than that of the nontransformed parental cells. However, transformed cells grown in medium containing these drugs did not show contact inhibition of cell division or increased agglutinability with Concanavalin A (Con A). The inhibition of growth was due to an extended duration of all phases of cell cycle. The protease inhibitor *N*- α -*p*-tosyl-L-lysine chloromethyl ketone HCl (TLCK), an active site titrant reacting irreversibly with trypsin, blocked transformed cells in the premitotic state of the cell cycle; this effect was not observed with the nontransformed parental cells. The decrease in agglutinability of transformed cells treated with TLCK was correlated with a partial synchronization in the G2 stage of the cell cycle. These data do not support the hypothesis that protease inhibitors induce transformed cells to assume a normal growth pattern, which is accompanied by a decreased agglutinability with plant lectins.

2305 DEATH IN NORMAL AND NEOPLASTIC CELLS. (E.) Wyllie, A. H. (Dept. Pathol., U. Edinburgh, Scotland). *J Clin Pathol [Suppl]* 27(7):35-42, 1974.

Two major modes of cell death occur among nonneoplastic cells: coagulative necrosis and apoptosis. Major cell injury is followed by the irreversible loss of homeostatic regulation, which is followed by a period of necrosis in which cellular constituents reach physiochemical equilibrium with themselves and their environment. This process, coagulative necrosis, usually involves sheets of cells at once, has never been conclusively demonstrated in the course of embryogenesis, and is probably not involved in the controlled regulation of cell populations. Apoptosis characteristically involves single cells whose neighbors remain viable and maintain the overall structure of the tissue in question. It occurs frequently in ontogenesis, at predictable times of development specifically deleting certain cells. It also occurs in postnatal tissues and can occur in situations where the environment is inclement but not so inclement as to cause coagulative necrosis. In at least some situations, apoptosis is probably a controlled, programmed event involved in tissue

homeostasis. Both modes of cell death occur among tumor cells. Apoptosis has been observed in human basal cell carcinoma of skin, squamous carcinoma of the uterine cervix, and experimental mammary tumors. In addition, it occurred early in an experimental tumor regressing after endocrine ablation. The latter finding supports the view that tumor cells, while relatively insensitive to normal tissue homeostatic mechanisms, are not devoid of intrinsic controls.

2306 ISOZYMES OF PYRUVATE KINASE IN LIVER AND HEPATOMAS OF THE RAT. (E.) Farina, F.

A. (Temple U. Sch. Med., Philadelphia, Pa.), J. B. Shatton, H. P. Morris and S. Weinhouse. *Cancer Res* 34(6):1439-1446, 1974.

Pyruvate kinase (PK) isozymes were assayed in normal rat liver and a series of transplantable rat hepatomas ranging widely in growth rate and degree of differentiation, with the use of gradient elution by chloride ion from columns of DEAE-cellulose. Three noninterconvertible forms were found in rat tissues: isozyme I, the major form in adult rat liver; isozyme II, the sole form in heart and skeletal muscle; and isozyme III, the sole form in poorly differentiated hepatomas, the major form in normal kidney and lung, and the minor form in adult liver. Although one highly differentiated hepatoma, 9618A, has a PK isozyme pattern similar to that of liver, other well- and highly differentiated hepatomas had much lower total activities than liver, with a preponderance of PK III. In contrast, the rapidly growing, poorly differentiated hepatomas had extremely high total PK activity, virtually all consisting of PK III. These results provide further evidence of a profound alteration of gene expression in hepatomas resulting in the loss of a specific liver-marker isozyme with loss of differentiation and its replacement in poorly differentiated hepatomas by high activities of an isozyme normally very low in the normal liver.

2307 STUDIES ON THE MECHANISMS OF INVASION IN CANCER. IV. A FACTOR ASSOCIATED WITH RELEASE OF NEUTRAL PROTEASE OF TUMOR CELL. (E.)

Kono, M. (Kumamoto U. Med. Sch., Japan), H. Katsuma and H. Hayashi. *Int J Cancer* 13(5):334-342, 1974.

A substance capable of releasing a neutral protease was isolated from transplanted ascites hepatoma cells in male Donryu rats, from 3-methylcholanthrene-induced mammary tumors in Sprague-Dawley rats, and from lymph nodes with metastatic mammary tumor cells. The substance, probably a thermostable peptide, can release the neutral protease very soon after contact with tumor cells, thus distinguishing it from the dialysable peptide occurring in the interstitial fluid of tumors or in the serum of tumor-bearing rats. As it is not cytotoxic, it is different from the protein found in acidified serum. Intradermal injection of the neutral protease isolated from hepatoma cells induced extravascular migration of circulating tumor

cells and formation of metastases. No protease was released from normal hepatic cells, even after 3 hr of observation. This suggests that the factor affects tumor cells and normal hepatic cells in different ways, perhaps due to functional differences on the surface of hepatoma and liver cells. The released neutral protease may be involved in malignant invasion through production of postulated cancer-cell-chemotactic factor. However, such a substance was difficult to demonstrate in normal skin. Different factors associated with the release of another neutral protease and an alkaline protease were also found. However, these proteases did not provoke invasion of tumor cells after intradermal injection.

2308 THE GRADED ENZYMIC IMMATURITY OF TRANSPLANTED NEOPLASMS. (E.) Knox, W. E. (Harvard Med.

Sch., Boston, Mass.). *Cancer Res* 34(8):2102-2108, 1974.

Analyses of the characteristic constituents were used to measure the degrees of chemical similarity among the tissues. Undifferentiated, fast-growing tumors originating from the rat liver and from mammary gland have almost the same composition. Differentiated tumors from the same sources are more unlike in compositions, each kind tending to resemble the chemically very different parent tissues. A prototypic composition of tumors, whatever the source, appears to exist. The prototypic composition of tumors is very similar but not identical to that of many fetal tissues in both the quantitative patterns of enzymes and the qualitative identities of certain isozymes. It appears that a fraction of the cell genome acts in the same way in immature and tumorous tissues but differently in adult tissues. Measurement of selected enzymes that are part, or are not part, of the prototypic composition of tumors can distinguish a variety of tumors from a variety of normal tissues. Relatively small numbers of enzymes (four or five) are sufficient to make this important distinction between the 24 normal and tumorous tissues examined.

2309 DISTINCT ALKALINE PHOSPHATASE IN SERUM OF PATIENTS WITH LYMPHATIC LEUKEMIA AND INFECTIOUS MONONUCLEOSIS. (E.) Neumann, H. (Pritzker

Sch. Med., U. Chicago, Ill.), E. M. Moran, R. M. Russell and I. H. Rosenberg. *Science* 186(4159):151-153, 1974.

Compared with controls, six patients with acute lymphatic leukemia (ALL), five patients with untreated chronic lymphatic leukemia (CLL), and 22 patients with infectious mononucleosis (IM) had an additional serum alkaline phosphatase. It had the same substrate specificity and the same electrophoretic mobility in polyacrylamide gel electrophoresis as the enzyme extracted from the thymus of mice with lymphatic leukemia; this alkaline phosphatase has been designated phosphatase N. For ALL, the range of phosphatase N was 26-100% of the total alkaline phosphatase activity; for untreated CLL, the range was 35-39%; and for active IM, the range was 23-100%. Alkaline phosphatase activity in nor-

mal serum was inhibited by serum of IM patients. The phosphatase N activity was related to the clinical state of the ALL and CLL patients and disappeared with recovery from IM. Measurement of phosphatase N in the sera of patients with lymphoproliferative diseases may be useful as an indicator of the presence and activity of the disease. It is likely that phosphatase N appears concurrently with other cellular changes associated with neoplastic transformation, especially in the case of CLL, and that the synthesis of phosphatase N is related to the presence of a virus.

- 2310 ABNORMAL SERUM ISOENZYME OF LEUCINE AMINOPEPTIDASE (LAP) IN MALIGNANT NEOPLASTIC DISEASE. (E.) Phillips, R. W. (VA Hosp., Spokane, Wash.) and E. R. Manildi. *Cancer* 34(2):350-357, 1974.

Leucine aminopeptidase (LAP) isoenzymes were studied in the serum and urine of 53 patients with various types of malignant neoplastic disease, and compared with those in a group of 23 normal controls. LAP isoenzymes in normal sera separated into two principal fractions, one designated X, migrating in the α 2 globulin range, and Y, migrating in the β globulin zone. Zymograms of the sera of patients with malignant neoplastic disease demonstrated a significant difference in the relative values of the X and Y fractions, compared with the normal controls. A progressive increase in the Y fraction developed in those whose neoplastic malignancy worsened. A decrease in peak height of the Y fraction occurred during periods of remission. It is suggested that the changes represent alterations in the total tumor cell mass of the patient. It is further suggested that the LAP isoenzyme zymogram may be of value as a diagnostic aid and a method of assessing the degree of remission or progression of a neoplastic process.

- 2311 CHARACTERIZATION OF LATE POLYOMA mRNA. (E.) Buetti, E. (Dept. Molecular Biol., U. Geneva, Switzerland). *J Virol* 14(2):249-260, 1974.

Polyoma-infected mouse kidney cell cultures were labeled with ^3H -uridine for 3 hr late in the lytic cycle (26-29 hr postinfection) and RNA was extracted from cytoplasm and nuclei and from isolated polyribosomes. Sedimentation velocity analysis in sucrose gradients showed that polyoma-specific 'giant' and 26S RNAs were present exclusively in the nucleus. RNA associated with cytoplasmic polyribosomes was analyzed by sedimentation in aqueous sucrose density gradients and dimethylsulfoxide sucrose gradients, as well as by polyacrylamide gel electrophoresis. Polyoma-specific RNA in the polyribosomes consisted of at least two classes, with sedimentation coefficients of 16 (major fraction) and 19S (minor fraction) in aqueous sucrose gradients and 15 and 17S, resp., in dimethylsulfoxide gradients. Estimates based on dimethylsulfoxide gradient analysis suggest molecular weights of approximately 500,000 for the 16S RNA and 700,000 for the 19S RNA. These polyoma RNAs seem to undergo reversible conformational changes

under the different analytical conditions. It is possible that they contain more than one molecular species.

- 2312 DEOXYNUCLEOTIDE-POLYMERIZING ENZYMES IN NORMAL AND MALIGNANT HUMAN CELLS. (E.) Srivastava, B. I. S. (Ruswell Park Mem. Inst., Buffalo, N.Y.). *Cancer Res* 34(5):1015-1026, 1974.

The cytoplasmic (175,000 $\times g$ supernatant) and the chromatin fractions from phytohemagglutinin-stimulated normal human lymphocytes, human thymus tissue, lymphocytes from chronic lymphocytic leukemia and acute lymphoblastic leukemia patients and cultured cells of normal (RPMI 1788), multiple myeloma (RPMI 8226), Burkitt lymphoma (HRIK), and acute lymphoblastic leukemia (Molt-4) origin were examined for deoxynucleotide-polymerizing enzymes by diethylaminoethyl cellulose and phosphocellulose chromatography, glycerol gradient centrifugation, and other properties. In all the cells examined, 6 to 7 S polyribosyladenyl acid-dependent polymerase, 3 to 4 S DNA-directed DNA polymerase, and 3 to 4 S terminal deoxynucleotidyl-transferase were found both in the cytoplasmic (latter two enzymes only in small amounts) and in the chromatin fraction; whereas 6 to 7 S DNA-directed DNA polymerase was found only in the cytoplasmic fraction. In glycerol gradients containing 0.1 M NaCl, the 6 to 7 S DNA-directed DNA polymerase and 6 to 7 S polyribosyladenylic acid-dependent DNA polymerase sedimented as 10 S aggregate and the 3 to 4 S DNA-directed DNA polymerase sedimented as the 7 S aggregate, whereas at 0.2 to 0.4 M NaCl they sedimented in unaggregated form. Both 3 to 4 S DNA-directed DNA polymerase and 6 to 7 S polyribosyladenylic acid-dependent DNA polymerase could give double peaks on diethylaminoethyl cellulose column. In addition to this examination of chromatographic and glycerol gradient behavior of enzymes, the template-primer and metal requirements and the effect of sulfhydryl inhibitors and monovalent cations were also studied.

- 2313 INFLUENCE OF GLUCOSE ON THE DEVELOPMENT OF EXPERIMENTAL METASTASES. (E.) Risca, R. (Oncol. Inst., Cluj, Romania) and C. Todorutiu. *Br J Cancer* 30(3):241-245, 1974.

Female Wistar rats were inoculated i.v. with Walker carcinosarcoma 256 cells (Group I) after being inoculated i.v. with a 10% glucose solution (Group II) or narcotized with thiopentone and then inoculated with 10% glucose (Group III). After tumor cell inoculation, the Group II and III rats were again injected with glucose. The incidence of tumor metastases was 50.9% in Group I, 83.6% in Group II, and 82% in Group III. Groups II and III developed significantly more tumors and after a slightly shorter latency than Group I; Groups II and III did not differ significantly from each other. In Group I, the tumors were localized in the lungs and lymph nodes, renal and ovarian metastases being rare. In Group II, the tumors were primarily found in the lungs, lymph nodes (tumors here being larger than in Group I), kidneys, and ovaries. The Group III rats developed pulmonary, lymph node, ovarian, renal, and

adrenal tumors. The data suggest that there may be a risk in using glucose in the intra- and post-surgical resuscitation of cancer patients.

- 2314 APPARENT CORRELATION BETWEEN ADENOSINE 3':5' CYCLIC MONOPHOSPHATE LEVELS AND MALIGNANCY IN SOMATIC CELL HYBRIDS. (E.) Tisdale, M. J. (St. Thomas's Hosp. Med. Sch., London, England) and B. J. Phillips. *Exp Cell Res* 88(1):111-120, 1974.

The intracellular concentrations of cyclic AMP (cAMP) were measured in A9H fibroblasts, TLX5 lymphoma cells, and hybrids between these two lines (A9T₄, A9H/TLX, and A9T₄/TLX). The cAMP levels in the cells correlated with their degree of malignancy in thymectomized CBA mice; the highly malignant parental cells had lower cAMP levels than the less malignant hybrids. There was no correlation between the growth rate of the cells in culture and their cAMP levels. Each cell type possessed cAMP phosphodiesterase with two K_m values: a low affinity form with K_m values ranging from 370-1055 μ M and a high affinity form with K_m values less than 5 μ M. The increase in cAMP observed was not due to a concomitant decrease in the activity of the phosphodiesterase since the specific activity at both K_m values increased with the intracellular cAMP concentration. The cells studied could be ranked as follows, in order of decreasing malignancy: TLX5, A9T₄/TLX, A9T₄, A9H, and A9H/TLX. The degree of contact inhibition of movement was inversely correlated with the degree of malignancy. The data support the view that intracellular concentrations of cAMP regulate the synthesis of cAMP phosphodiesterase and that cAMP functions as an inducer of the enzyme.

- 2315 THE NUCLEOTIDE SEQUENCES OF CYTOPLASMIC METHIONINE AND VALINE tRNAs FROM MOUSE MYELOMA CELLS. (E.) Piper, P. W. (Med. Res. Council, Cambridge, England) and B. F. C. Clark. *FEBS Lett* 47(1):56-59, 1974.

Cytoplasmic methionine and valine tRNAs (tRNA^{met}₄ and tRNA^{val}) were purified from the post-microsomal supernatant fraction of mouse P3K plasmacytoma cells cultured in medium containing ³²P-phosphate. Mouse myeloma tRNA^{met}₄ is 76 nucleotides in length and possesses 15 modified nucleosides. Sequence analysis indicated that all the nucleoside modifications of tRNA^{met}₄ were complete except for the methylation of the cytidine within the anticodon; this was 60-80% complete. This is the first tRNA which possesses the minor nucleoside m²G within the stem of its cloverleaf; it also possesses two pseudouridine nucleosides in opposite positions at the base of stem. Thus, this species probably has a stem comprised of 5 base-pairs. The unusual loop IV sequence, -A-U-C-G-m'A-A-A-, of eukaryotic initiator tRNAs was not found in this methionine tRNA, which functions in protein elongation. tRNA^{val} is also 76 nucleotides in length. Its loop IV sequence, -U-Ψ-C-G-m'A-A-A-, is unique among known tRNA primary structures. It also possesses the minor nucleoside m²G at a position within stems of the cloverleaf. The loop III sequence, -A-G-m⁷G-D-m⁵C-, is found in both tRNA^{met}₄ and tRNA^{val}. The nucleotide structures of tRNA^{met}₄ and tRNA^{val} are compared with those of other known tRNAs.

- 2316 OLIGONUCLEOTIDES OF RIBOSOMAL 28 S RNA IN HUMAN LEUKEMIC CELLS AND NORMAL LYMPHOCYTES. (E.) Seeber, S. (U. Clin., Essen, W. Germany), K. P. Brucksch, J. Kading, C. G. Schmidt and H. Busch. *Cancer Res* 34(6):1281-1288, 1974.

Ribosomes were isolated and ribosomal RNA (rRNA) was prepared from leukemic cells derived from the venous blood of patients with acute myeloblastic leukemia, acute undifferentiated leukemia, subacute myelocytic leukemia, chronic lymphocytic leukemia, leukemic lymphosarcoma, leukemic reticuloendotheliosis, a cultured Burkitt lymphoma cell line, and phytohemagglutinin-stimulated normal lymphocytes. After *in vitro* labeling of the cells for 9 hr with orthophosphate-³²P, the 28 S rRNA was characterized by nucleotide analysis and by oligonucleotide frequency studies on dinucleotides and trinucleotides released by complete digestion with pancreatic RNase. Under identical labeling conditions, there was a significant difference in the specific activities of the 28 S rRNA of acute myeloblastic leukemia cells and phytohemagglutinin-stimulated lymphocytes. Following separations of the oligonucleotides of the RNase digests on DEAE-Sephadex A-25 at pH 7.6 according to chain length, minor variations were found in the oligonucleotide frequencies of 28 S rRNA within this group of leukemias; but there were no significant differences from the values for phytohemagglutinin-stimulated lymphocytes. Thus, in these cells, as in animal tumors, there is a remarkably constant composition and structural similarity of 28 S rRNA.

- 2317 TRANSFER RIBONUCLEIC ACID SPECIES IN NORMAL AND LEUKEMIC LEUKOCYTES. (E.) Rainer, H. (U. Vienna Med. Sch., Austria), P. Hocker, A. Stacher, K. Moser, I. Streit and E. Deutsch. *Neoplasma* 21(4):409-414, 1974.

The tRNA concentrations in normal leukocytes and leukocytes from patients with chronic myeloid leukemia were compared using a cochromatographic technique. The number of tRNA species was identical in both types of cells. Elution profiles of leukemic cells showed the presence of species with chromatographic behavior both analogous to and different from that of normal cells. Of the species with analogous patterns, the acceptor activity of the alanyl, arginyl, lysyl, ethionyl, and valyl-tRNAs of the normal cell tRNA species was less pronounced than that of the corresponding species of the leukemic cells. Only for the phenylalanine-accepting tRNA species was the acceptable potential of the normal cells greater than that of the corresponding leukemic cell species. Leukemic cell tRNA species with a modified chromatographic behavior were the aspartyl, leucyl, threonyl, glycyl, seryl, and tyrosyl RNAs.

- 2318 CORRELATION OF (Na⁺-K⁺)-ATPASE ACTIVITY WITH GROWTH OF NORMAL AND TRANSFORMED CELLS. (E.) Elligsen, J. D. (Dept. Biol., U. Waterloo, Canada), J. E. Thompson, H. E. Frey and J. Kruuv. *Exp Cell Res* 87(2):233-240, 1974.

The (Na⁺-K⁺)-stimulated Mg²⁺-dependent ATPase activi-

ties of 3T3 and simian virus 40 (SV40)-transformed 3T3 cells were compared as a function of cell population density. For normal cells, the enzyme activity remained relatively constant during exponential growth, but decreased sharply during contact inhibition of growth at confluence. This decrease in activity could be reversed by stimulating the contact-inhibited cultures to undertake renewed short-term growth either by adding fetal calf serum or by changing the medium completely. The transformed cells did not experience a decrease in $(\text{Na}^+-\text{K}^+)\text{-ATPase}$ activity upon reaching confluence, but this is consistent with the fact that they were still growing exponentially at this stage. However, nonconfluent cultures of both normal and transformed cells showed a marked decrease in the levels of the enzyme when growth was inhibited by serum depletion. The results suggest that $(\text{Na}^+-\text{K}^+)\text{-ATPase}$ levels in both normal and transformed cells are correlated with growth. Thus, the different patterns of ATPase activity exhibited by malignant cells and their normal counterparts with increase in cell number appear to be a reflection of their dissimilar growth patterns rather than of any innate difference between them.

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2030, 2090*	2205*	1999*
ARMSTRONG, D.Y.	ANDREONE, T.L.	BARTRELLI, A.
1879	1921*	2225*
ARMSTRONG, S.F.	ANDREWS, F.J.	BASS, E.M.
1967*	1849, 2114	2233*
ARMSTRONG, A.	ANKERST, J.	BAST, R.C., JR.
2394*	2138	1878
ARMSTRONG, D.	ANTEUNIS, A.	BASTIEN, H.
2072	2147	1828
ARMSTRONG, D.V.	APPELLA, F.	BATAILLON, G.
2065	2189	2023
ARMSTRONG, R.J.	APPLEBY, F.C.	BATTULA, N.
2181, 2196*	1991*	2048
ARMSTRONG, R.	ARAI, M.	BAJM, S.G.
2225*	1877	2033
ARMSTRONG, B.	ARCHER, D.L.	BEAL, D.D.
2207*	2050	1945*
ARMSTRONG, J.	ARGYRIS, T.S.	BEAUMONT, E.
1947	1884	2232*
ARMSTRONG, F.	ARLEN, M.	BECKER, D.V.
2064	2023	2005
ARMSTRONG, J.T.	ARMENIAN, H.K.	BECKER, F.F.
2076*	2250	2122
ARMSTRONG, M.J.	ARMENIO, L.	BECHRENS, R.C.
2365*	2121	1952*
ARMSTRONG, M.	ARMSTRONG, B.	BEN-BASSAT, M.
2322*	1860	2216*
ARMSTRONG, A.C.	ARMSTRONG, G.	BEN, T.L.
2168	2072	1978*
ARMSTRONG, M.	ARNSTEIN, P.	BENASSI, G.
1845	2090*	2136
ARMSTRONG, H.	ARTHUR, M.	BENINI, A.
2381*	2279	2328*
ARMSTRONG, A.	ASH, R.J.	BENTONOVICH, M.S.
1923*	2093*	1809
ARMSTRONG, R.E.	ASHLEY, D.J.R.	BENNETT, S.
1956*, 1973*	2287*	2244*
ARMSTRONG, R.	AUGUST, J.T.	BENYESH-MELNICK, M.
2188	2031	2029
ARMSTRONG, D.J.	AYRE, J.F.	BERENDES, U.
2035	2372*	1812
ARMSTRONG, M.	BABA, K.	BERGET, A.
2046	2321*	1839
ARMSTRONG, P.	BACK, A.F.	BERNHARD, H.P.
2153	2175	2297
ARMSTRONG, A.C.	BAIRD, W.M.	BERNIER, G.M.
1805, 1847	1971*	2373*
ARMSTRONG, J.	BALDWIN, R.W.	BERNSTEIN, H.
1829, 1861	2165	2207*
ARMSTRONG, N.H.	BALICK, R.	BERTI, G.
1998*	1854	2136
ARMSTRONG-FUERTES, G.	BALIS, M.E.	BERTINI, R.
2240*	1933*	2245*
ARMSTRONG, U.	BALL, F.L.	BERTOLINI, L.
2280	2152	2299
ARMSTRONG, R.	BALLAS, M.	BERTRAM, J.S.
2321*	2119	1908*
ARMSTRONG, T.	BALMAIN, A.	BEZDEK, M.
2369*	1888	2337*
ARMSTRONG, L.F.	BANATWALA, T.	BIANCIO, M.A.
2319*	2212*	2134
ARMSTRONG, G.P.	BANERJEE, M.P.	BIJLSMA, F.
2030	1916*	2258
ARMSTRONG, J.M.	BARRON, R.	BILGER, L.
1822*	2070	1973*
ARMSTRONG, N.G.	BARTHOLO, S.W.	BINGHAM, E.
2152	2184	1994*

BIRCH, N. 1972*	BREILLATT, J.P. 2152	BURLINGHAM, B.T. 2053
BISCHOFF, F. 1902*, 1903*	BREINL, H. 2251*	BURMEISTER, H.R. 1833
BISHOP, J.M. 2016	BREITBURD, F. 2062	BURN, J.I. 2376*
BLACKMAN, K.E. 2173	BREMER, K. 2224*, 2368*	BURNS, F.J. 1955*, 1969*, 1973*
BLAIR, C.D. 2029	BRENNAN, P.J. 2029	BURRY, A. 2083*
BLAIR, W.H. 1962*	BRENNER, H.J. 2127	BUSCH, G.E. 1913*
BLAU, S. 2112	BRESNICK, E. 1930*	BUSCH, H. 1913*, 2315
BLAUSTEIN, A. 2296	BRILES, W.E. 2212*	BUSH, I.M. 2191, 2196*
BLONSTEIN, S.H. 1976*	BRONSDON, A. 2009	BUTEL, J.S. 1807
BLUMBERG, F. 2154	BROOKES, P. 1971*	BUTTERFIELD, A. 1847
BODDION-PALLAVICINI, E. 2201*	BROSS, I.D.J. 2250	BUXBAUM, J.N. 2131
BOCK, F.B. 1926*	BROWN, A. 2078*	CAMERON-MOWAT, D.E. 2234*
BODDANOFF, E. 2188, 2279	BROWN, C.A. 1900*	CAMPBELL, J.C. 2107*
BODENHAGEN, D. 2366*	BROWN, D.T. 2063	CAMPBELL, M.J. 2116, 2294
BODGLEANU, N. 2252*	BROWN, E.R. 1917*	CAMPBELL, T.C. 1848
BODICCHI, M. 1842	BROWN, G. 2343*	CANDELLAS, G. 1930*
BODIHJIS, R.L.H. 2129	BROWN, R. 2173	CANDLER, E.L. 2152
BOLGNEST, D.P. 2027, 2031	BROWN, R.C. 1947*	CAPOFERRI, R. 1882
BOLTON, P.M. 2231*	BROWNSTEIN, S. 2354*	CARDESA, A. 1829
BONE, G. 2237*	BRUCHER, J.M. 1841	CARDIFF, R.D. 2077*
BONNET, C. 2125	BRUCKSCH, K.P. 2316	CARNAJO, C. 2193*
BORNSTEIN, R.S. 2239*	BRYAN, G.T. 1907*, 1950*, 1952*	CARTER, B.J. 2073*
BORSOS, T. 1878	BRYSON, G. 1902*, 1903*	CARTER, R.L. 2384*
BOSMANN, H.A. 2037	BUG-CARDON, M.-H. 2156	CARVAJAL, G. 2240*
BOYD, A. 2395*	BUCHAN, R. 2344*	CASTELL, D.D. 2352*
BOYD, A.L. 1807	BUCHSBAUM, R. 2068	CASTO, B.C. 2034
BOYD, H. 1893	BUCHOVAZ, E.T. 1965*	CATON, J.E. 2152
BOYLAND, E. 1934	BUETTI, F. 2311	CATOVSKY, D. 2219*
BOYNS, A.R. 2344*	BUKRINSKAYA, A.G. 2028	CAUCHI, M.N. 2155
BOYNTON, A.L. 2298	BULBA, S. 1998*	CAVALIERI, E. 1906*
BOYSE, E.A. 2075*, 2171	BURCULET, V. 2252*	CAWLEY, J.C. 2085*
BRADA, Z. 1998*	BURGESS, M.A. 2110	CAYPHAS, J. 2400*
BRADSHAW, E. 2269	BURGIO, G.R. 2140	CECI, A. 2121
BRAJNSBERG, H. 2396*	BURKI, K. 1930*	CERNAT, M.J. 2255*

CHALLIS, R.C.	COHEN, M.M.	CURTIS, G.L.
1992*	2020	1924*
CHAN, P.C.	COHEN, N.D.	CURTIS, L.E.
1958*	1919*	2195*
CHAN, S.W.C.	COHEN, S.M.	CZEIZEL, A.
1953*	1950*	2276
CHANG, Y.	COLBURN, N.H.	DACO, R.
2213*	1904*	1962*
CHAPUT, B.	COLE, E.N.	DAHLBERG, J.
2179	2344*	2079*
CHARLES, R.T.	COLLARD, J.G.	DAILY, N.H.
1842	2304	2243*
CHAWDA, R.	COMMONER, B.	DALE, M.M.
2068	2009	2166
CHEN, B.L.	COMMONS, P.M.	DANIEL, B.G.
2217*	2069	1954*
CHEN, H.C.	CONGER, B.	DANPURE, C.J.
1838	2070	2001
CHEN, H.W.	CONNOLLY, C.E.	DADUD, A.H.
2115	2381*	1974*
CHEN, Y.C.	CONSIGLI, R.	DARLINGTON, G.J.
2044	2078*	2297
CHEERY, M.	CONSIGLI, R.A.	DARMALINGAM, S.
2115	2054	2150
CHESEBRO, B.	COOK, C.	DAS GUPTA, T.K.
2098*	1886	1957*, 1977*
CHIRIGOS, M.	COOMBS, M.M.	DAS, S.B.
2075*	1970*	1925*
CHISAKA, N.	COOPER, N.R.	DAVE, C.
1880	2053	1941*
CHIURCO, G.A.	CORBETT, M.D.	DAVIDSON, J.
2281*	1858	2231*
CHOPRA, D.P.	CORE, S.K.	DAVIDSON, J.F.
2010	1949*	2329*
CHU, T.M.	CORK, A.	DAVIES, A.J.S.
2180	2365*	2219*
CHAK, R.W.	CORNBLEET, P.J.	DAVIES, R.F.
2274	2331*	1835
CLARK, R.F.C.	COTTLER-FOX, M.	DAVIES, W.A.
2315	1878	2200*
CLARK, H.F.	COVERLIZZA, S.	DAVIEW, P.
2020	2273	1847
CLARKSON, B.D.	CRAILLY, L.J.	DAVIS, D.B.
2278	1895	2068
CLAYTON, D.A.	CREASY, R.K.	DAWSON, P.J.
2366*	1911*	2024
CLEMETT, A.R.	CRINGU, M.	JAY, N.F.
2319*	2261*	2150
CLINE, M.J.	CRISPIN, R.G.	JAY, N.K.
2145	2241*	2228*
COALSON, J.J.	CRISTEA, A.	DE BARBIERI, A.
2177	2375*	2225*
COALSON, R.E.	CROCE, C.M.	DE ENGELSE, L.
2177	2022, 2043	1816
COCHRAN, A.J.	CROCKER, T.T.	DE LIMA, C.G.
2234*	1911*, 2006	1897
COEZY, F.	CROFT, W.A., JR.	DE NOTTER, W.
1997*	1945*	2218*
COFFIN, J.M.	CROISSANT, O.	DE-THE, G.
2040	2062	2150
COGGIN, J.H., JR.	CUBIE, H.A.	DE VOOGT, H.J.
2152	2087*	2385*
COHEN, C.	CULBRETH, K.	DE YOUNG, L.
1977*	2027	1884
COHEN, I.R.	CUPP, J.J., JR.	DECARVALHO, S.
2193*	2017	2242*
COHEN, L.A.	CURTIS, J.P.	DECKERS, C.
1958*	1840	1836

DECKERS-PASSAU, L. 1936	DUFFIELD, R. 2195*	FARROW, J.H. 2288
DECLEVE, A. 2133	DUFNOR, J.J. 2394*	FAVRE, M. 2052
DEFENDI, V. 2039	DULLENS, H.F.J. 2218*	FELDMAN, J.D. 2014
DEHNER, L.P. 2345*	DUNKEL, V.C. 1878	FELDMAN, M. 2193*
DELAFFOND, F. 2325*	DUNN, A.R. 2108*	FELDMANN, M. 2204*
DEMETRIDOU, J. 1964*	DURAN-REYNOLDS, M.L. 1886	FICHT, D. 2400*
DEMPD, K. 1880	DUTU, R. 2252*	FIELDSTEEL, A.H. 2024
DENDA, A. 1877	DUX, A. 2084*	FIERS, W. 2092*
DENG, C.S. 1838	DWORSKY, R.L. 2270	FILFS, J.G. 2041
DENTON, P.M. 2236*	DYBKJAER, F. 2198*	FINK, C.G. 2387*
DESAI, H.N# 2165	DZIKIDZE, E.K. 2339*	FINK, L.M. 1987*
DESAI, P.R. 2212*	EASTY, G.C. 1808	FINK, U. 2137
DESHPANDE, D. 2376*	EBINA, T. 2047	FISCHER 2388*
DEUTSCH, F. 2317	EDWARDS, G.S. 1909*	FISH, S.A. 1965*
DIAMOND, E.L. 2250	EL MASRY, N.A. 2352*	FLAD, H.D. 2358*
DICK, V.S. 2249	ELIAS, E.G. 2292	FLAX, I. 2377*
DIERLAM, P.J. 2152	ELLIGSEN, J.D. 2318	FLEISSNER, E. 2031
DIETZSCHOLD, B. 2175	EMBLFON, M.J. 2165, 2230*	FLESHER, J.W. 1959*
DIKUN, P.P. 1803	EMMELOT, P. 1816	FLOYD, R.A. 2009
DIPADLO, J.A. 1920*, 2034	ENEROTH, C.M. 2379*, 2380*	FONG, J.A. 1934*
DIPPLE, A. 1971*, 1982*	ENGESFT, A. 2224*	FORBES, P.D. 1966*, 2010
DIWAN, B.A. 1852	ENNIS, F.A. 2172	FORNES, M.F. 2352*
DOBYNS, B.M. 2005	EPSTEIN, S.S. 1923*	FORREST, A.P.M. 2320*, 2344*, 2395*
DOEFER, W. 2063	ERECINSKA, M. 2355*	FORT, L. 1841
DOEFER, W. 2097*	ESCHBACH, W. 2094*, 23864	FOWLER, A. 2365*
DOLL, R. 1860	ESTERLY, J.A. 2331*	FOX, K.A. 1855
DONOVAN, P.J. 1920*	EVANS, C.H. 1939*	FOX, R.I. 2033
DRAKIN, M.S. 2189	EVFLIGH, J.W. 2152	FRANK, H. 2091*
DRASAR, D.S. 1825*	EVERSE, J.W.R. 1890	FRANKLIN, E.C. 2131
DRILL, V.A. 1870	EZDINLI, F. 2292	FRANKS, L.M. 2397*
DRLICA, K.A. 2370*	FAGAN, V. 1975*	FRAZIER, J.A. 2051
DRUGER, F.W. 1829	FAIRBURN, F.A. 2383*	FRFIREICH, E.J. 2110, 2158, 2280
DUPLESSIS, D.J. 2246	FARID, Z. 2352*	FREY, H.E. 2318
DJANE, M.P. 1866	FARINA, F.A. 2306	FRIBERG, S. 2303

FRIDLENDER, B.	GHADIALLY, F.N.	GREENWOOD, M.F.
2112	2360*	2209*
FRIED, M.	GHOSH, B.C.	GREY, H.M.
2350*	1957*	2215*
FRIEDMAN, L.	GHOSH, L.	GRIGUREVIC, M.
2300	1957*	2264
FRIEDMAN, M.A.	GILDEN, R.V.	GRIFFITHS, C.
1883	2018, 2031	2343*
FRIIS, R.R.	GILLETTE, R.W.	GRIFFITHS, K.
2044	2173	2344*, 2359*
FROLAND, S.S.	GILLI, J.	GRJNOW, M.
2224*	2126	1859, 1995*
FJ, Y.-S.	GILLIAM, E.B.	GROSSBERG, A.L.
1810	2211*	2160
FUCHS, R.P.P.	GILLIS, C.R.	GROVER, P.L.
1866	1824*	1971*
FUJI, K.	GILLISSEN, G.	GRUFENSTEIN, M.
1853	2135	1954*
FUJIMURA, S.	GIRARDI, A.J.	GRUNBERGER, D.
1851, 2374*	2043	1976*
FUJITA, D.J.	GLATHE, H.	GSCHWIND, C.R.
2044	2094*	2158
FUJITA, H.	GLAZER, R.I.	GJERIN, D.
2327*	1937*	1840
FJKUSHIMA, M.	GLOVER, E.	GUINAN, P.
2157	1839	2181, 2196*
FURUNO, A.	GO, V.L.W.	GURTOD, H.
2036	2151	1941*
GABRIELA, S.	GOEPFERT, H.	GUTMANN, H.R.
2255*	2064	1912*
GACHELIN, G.	GOLDBLATT, H.	GUTTERMAN, J.U.
2156	2300	2110, 2158
GAGNON, H.J.	GOLDE, D.W.	HAAS, H.
1989*	2146	1857
GAHRTON, G.	GOLDEN, R.L.	HACHMEISTER, J.
2289	1844	2256*
GAILANI, S.	GOLDENBERG, D.M.	HADLER, H.T.
2292	2111, 2293	1954*
GALESLOOT, J.	GOLDTHWAIT, D.A.	HAGLID, K.G.
2133	1864	1874
GALLEZ, G.	GOLESKI-REILLY, C.	HAKULINEN, T.
1996*	2170	2252
GALLIMORE, P.H.	GOLFERINI, A.	HALLOWES, R.C.
2108*	2225*	2378*
GALLO, R.C.	GOMARD, E.	HAMDY, F.
2056	2197*	2042
GAMLEN, T.R.	GOOD, R.A.	HAMILTON, J.M.
2392*	2139, 2228*	1995*
GARCIA, H.	GOODBODY, R.A.	HAMPRECHT, B.
1906*	2392*	2340*
GARCIA, Y.	GOODWIN, B.J.	HANCOCK, R.L.
2232*	2264	1876
GARDONYI, J.	GORBACHEVA, L.B.	HANNUKSELA, M.
2276	1879	2163
GATI, F.	GORDON, G.	HANSEN, H.J.
1842	1884, 2335*	2111, 2164
GAUTHIER, J.M.	GOTH, R.	HANSEN, P.J.
1836	1865	2200*
GEORGE, S.L.	GRAHAM, R.C.	HARA, K.
2280	2373*	1936*
GEORGIADIS, A.	GRANT, R.M.	HARAN-GBERA, N.
2164	2234*	2045
GERKINS, V.R.	GRAVELLE, I.H.	HARINGTON, J.S.
2279	2320*	2285*
GERSTL, B.	GREAGER, J.A.	HARMS, D.
2277	1977*	2210*, 2229*
GERWIN, B.I.	GREENWALD, P.	HARNDEN, D.G.
1878	2249	2383*

HARRISS, E.B. 2363*	HENNINGS, H. 1905*	HUEBNER, K. 2022, 2043
HART, F.R. 1870	HERBERMAN, R.R. 2185, 2187	HUEBNER, R.J. 2030*
HART, J.S. 2280, 2365*	HERMAN, M.H. 2334*	HUGGINS, C.R. 1891
HARTZ, S.C. 1862	HERSH, F.M. 2110, 2158	HUGHES, D. 2116
HARVEY, R.G. 1976*	HEUSON, J.C. 1996*	HUGHES, L.E. 2231*, 2235*
HASEGAWA, S. 2374*	HEWITT, H.B. 2353*	HUMES, J.L. 2017
HASHIMOTO, Y. 1830	HIJMANS, W. 2129	HUMPHREY, L.J. 2148
HATAKAKA, M. 2218	HILF, R. 1919*	HUNG, P. 2074*
HATTLER, B.G., JR. 2117	HILFRICH, J. 1857	HUNSMANN, G. 2091*
HAWKSWORTH, G. 1843	HILGERS, J. 2133	HUNTER, C. 2110
HAYASHI, H. 2307	HILL, M.J. 1825*, 1843	HUOT, L. 2394*
HAYASHI, T.T.A. 2174	HIRAI, K. 2039	HYMAN, R. 2199*
HAYES, J.R. 1848	HIRAO, K. 1877	ICHIKAWA, M. 1952*
HAYFLICK, L. 1968*	HO, H.C. 2150	IGARASHI, A. 1831
HAZDRA, J.J. 1917*	HOCH, W.S. 2335*	IKEOA, H. 2075*, 2190
HEADLEY, D.A. 1950*	HOCKER, P. 2317	INDO, K. 1980*
HEALY, T.M. 2389*	HOD, I. 2013	IOKI, Y. 1835
HEBERLING, R.L. 2095*, 2096*	HOFFMANN, E.K. 2351*	IRVING, C.C. 1974*
HECKER, E. 1888	HOFNUNG, M. 2156	IRWIN, R. 2075*
HEDGCOCK, C. 2054	HOGETVEIT, A.C. 1999*	ISAACS, R.J. 2298
HEIDELBERGER, C. 1908*	HOLGAARD, K. 2198*	ISHIKAWA, G. 1811
HEIMANN, R. 1996*	HOKAMA, A. 2157	ISHIKAWA, Y. 2157
HEINE, U. 1878	HOLBOROW, E.J. 2219*	ISHIKO, S. 2356*
HEINIGER, H.J. 2115	HOLLADAY, D.W. 2152	ISHIMARU, T. 2274
HEINONEN, O.P. 1862	HOLLAND, P. 2209*	ISHITANI, R. 2025
HEINRICH, P.C. 2341*	HOLLEMAN, J.W. 2152	ISRAEL, L. 1817
HELOER, A.W. 2013	HOLT, S.C. 2042	ITO, N. 1877
HELMKE, R.J. 2095*, 2096*	HOLYOKE, E.D. 2180	ITOH, U. 2038
HELSON, L. 1928*	HOPP, M. 1961*	IVANOV, M.T. 2339*
HENOERSON, B.E. 2188, 2270, 2279	HORIKAWA, M. 2374*	IZSAK, F.C. 2127
HENDIL, K.B. 2351*	HOROUPIAN, O.S. 2324*	IZUMI, T. 1831
HENLE, G. 2188	HOW, S.W. 1838	JACOB, F. 2155
HENLE, W. 2188	HRADEC, J. 2061	JACOBSON, E.L. 2054
HENNER, D. 2039	HUBNER, G. 2390*	JAGUEUX, M. 2400*

JAMES, S.L. 2231*	KALTER, S.S. 2095*, 2096*	KIRKBRIGHT, G.F. 1897
JANSS, D.H. 1978*	KAMEI, Y. 2290	KIRMASS, V. 2249
JARRFTT, W.F.H. 1983*	KAMEYA, T. 2322*	KIRTIKAR, D.M. 1864
JASTY, V. 1960*	KANABATAKE, T. 2000	KLOPFER, U. 2013
JAVADPOUR, N. 2120	KANAGALINGAM, K. 1933*	KNAPP, R.C. 2253*
JELEN, S. 2046	KANAZAWA, I. 2393*	KNAPP, W. 2129
JENG, D.Y. 2213*	KANDUTSCH, A.A. 1876	KNOBEL, S. 1828
JENNER, D.A. 2359*	KANEKO, A. 1880	KNOPF, J.-F. 1828
JENSEN, F. 2014	KANISAWA, M. 1845	KNOX, W.E. 2308
JESSUP, J.M. 1928*	KAPLAN, H.S. 2133	KNJDSON, A.G., JR. 2247
JICK, H. 1862	KARPAS, A. 2085*	KODAMA, M. 1835
JOHANSSON, H. 2371*	KASPEREK, K. 2358*	KOGURE, K. 1851
JOHNSON, B.E. 1823*	KATARIYA, R.N. 2320*	KOHEN, C. 2362*
JOHNSON, G.S. 2032	KATO, H. 1867	KOHEN, F. 2362*
JONES, I.G. 2330*	KATSUYA, H. 2307	KOTIDI, T. 2321*
JONES, J.M. 2014	KAUFMAN, D.G. 1990*	KOJIKI, M. 2157
JONES, K.W. 2108*	KAUSCH, O. 2144	KOKA, M. 1979*
JONES, R.F. 1975*	KAWACHI, T. 1851	KOLB, J.P. 2178
JONES, T. 2359*	KEEFF, D.A. 1909*	KOMATSU, S. 2374*
JORDAN, J.J. 1913*	KEITH, L. 1917*	KONISHI, Y. 1901*
JORDON, R.E. 2228*	KELLICUTT, L.M. 1869	KONNO, M. 2307
JORNVAL, H. 2088*	KELLY, L.S. 2011*	KOPROWSKI, H. 2022, 2043
JOSEY, W.E. 2265	KENNEDY, A.R. 1871	KOREK-AMOROSA, J. 2319*
JOSHI, S.R. 1922*	KENNEDY, B.J. 1986*	KOSTYU, J.A. 1947*
JOSHUA, H. 2216*	KERSON, L.A. 2324*	KOTHARI, R. 2074*
JUAREZ, H. 2054	KESSLER, I.I. 2264	KOUTTAS, N.M. 2220*
JUSTRABO, E. 1828	KHOO, S.K. 2161	KOYAMA, S. 2369*
JUTILA, J.W. 2220*	KIANG, D.T. 1986*	KRANZL, B. 2391*
KAADEN, O.R. 2176	KIKUCHI, A. 2157	KREBS, B. 2126
KADING, J. 2316	KILGORE, A. 1947*	KREIBICH, G. 1887
KADJ, C.I. 2370*	KILLIAN, H.A. 2243*	KRUEGER, R.G. 2191, 2202*
KAFHLER, S.L. 2049	KIMMFL, C.B. 2226*	KRUGER, F.W. 1851
KAISERLING, E. 2145	KING, C.M. 1942*	KRUUV, J. 2318
KALISS, N. 2115	KINZFL, V. 1887	KUBICKOVA, D. 2337*

KUBINSKI, H. 1869, 1946*	LAZARIDES, E. 2041	LITMAN, G.W. 1873
KURD, R.T. 2215*	LE MAREC, M. 1840	LITMAN, R.J. 1873
KUBOTA, H. 2374*	LEATHEN, J.H. 1953*	LITTLE, J.B. 1871
KUCENCO, N.G. 1879	LEBEDEVA, F.N. 2028	LIVINGSTON, R.B. 2280
KULCAR, Z. 2264	LECLERC, J.C. 2197*	LO GERFO, P. 2244*
KUPCHIK, H.Z. 2169	LEE, C. 1961*	LO, K.W. 2125
KURIHARA, M. 1831	LEF, P.N. 1885	LOCKWOOD, T. 2037
KURITA, S. 2290	LEFFERT, H.L. 2122	LODISH, H.F. 2021
KURODA, K. 1845	LEGNOS, N. 1996*	LOER, L.A. 2048
KUWABARA, N. 1951	LEGUERRIER, J.M. 2372*	LONG, J.C. 2168
KUWATA, T. 2026	LEHTIMAKI, L. 2262	LORENTZEN, R.J. 1929*
KWOCZYNSKI, M.Z. 2257*, 2398*	LEHTONEN, M. 2262	LOUIE, E. 2188
LA PLANT, P.R. 2011*	LEITH, R.S. 1968*	LOUIS, C.J. 1893
LACHEN, R.B. 1856	LEJEUNE, F.J. 2232*	LOVE, R. 2348*
LACHER, M.J. 2381*	LEDNARD, F.J. 2159	LJWENTHAL, M.V. 2330*
LAGERLOF, B. 2258*	LEPPALUOTO, P. 2399*	LOWER, G.M., JR. 1907*
LAKSHMI, M.S. 2302	LERMAN, M.I. 1879	LUCAS, F.V. 2331*
LAM, P. 2058	LESKO, S.A. 1929*	LUFTIG, R.B. 2027
LAMM, M.E. 2171	LESLEY, J. 2199*	LUND, J. 2077*
LAMPRECHT, F. 2340*	LESPINATS, G. 2178	LUTZEYER, W. 2135
LANDES, E. 2127	LEVINE, F.M. 2213*	MACE, F. 1836
LANDOLT, A. 2328*	LEVINE, P.H. 2158, 2185	MACHIDA, S. 2157
LAPIN, B.A. 2339*	LEVY, J.P. 2197*	MACKAY, E.V. 2161
LAPIS, K. 2338*	LEWIS, A.J. 2243*	MACKIE, R.M. 2234*
LARABEE, K.L. 2226*	LEWIS, D.J. 2378*	MACLAURIN, B.P. 2222*
LARSON, D.L. 2053	LI VOLSI, V. 2244*	MACLEOD, M.C. 2326*
LAU, S. 1904*	LIFBERMAN, M.W. 1940*	MADISON, R.M. 1948*
LAU, T.J. 1895	LIEBSCHER, S. 2206*	MAGEE, P.N. 1820*
LAUDER, I. 2237*	LILIENFELD, A.M. 2250	MAGRATH, I.T. 2143
LAUSCH, R.N. 2186	LILLEHOJ, E.B. 1833	MAHER, V.M. 1972*
LAW, L.W. 2189	LINDEMANN, J. 1801	MAISIN, J. 1836
LAWRENCE, H.S. 2288	LINDENFELSER, L.A. 1833	MAKINO, F. 1858
LAWSON, D.H. 1862	LINDSTEIN, J. 2289	MAKIURA, S. 1877
LAWSON, T.A. 1827	LINKHART, S.G. 1934*	MALY, A. 2061

MANILOI, F.R. 2310	MCKENNA, P.J. 2319*	MISTRETTA, A.P. 2225*
MANVING, D.D. 2220*	MCLEAN, A.E.M. 1896	MITSUMO, T. 1875
MARCARJAN, D.S. 2339*	MCMTLLAN, P.N. 2027	MIVAKI, K. 1845
MARQUARDT, H. 1931*, 1932*	MEDEIROS, F. 2016	MIYAMOTO, M. 1892
MARSAN, C. 2400*	MEDINA-SANTILLAN, R. 2240*	MOFNNIG, V. 2091*
MARTIN, A.P. 2331*	MEYER, H. 1852, 2115	MOERTEL, C.G. 2151
MARTIN, D.P. 1870, 2182	MELANDRI, P. 2136	MOHR, J.A. 2177
MARTIN, F. 1828	MELCHERS, F. 2205*	MOHR, U. 1829, 1855, 1857
MARTIN, M.S. 1828	MELKI, G. 2332*	MOLNAR, J. 2303
MARTIN, T.J. 1893	MELLORS, R.C. 2076*	MOORE, D.H. 1819*, 2071
MASON T.J. 2266	MELNICK, J.L. 1807	MOORE, G.E. 2033
MASSEYEFF, R. 2126	MELTON, J.W., III 2141	MOORE, R.D. 1951*
MASSICOT, J. 2075*	MELVILLE, E. 2396*	MORAN, E.M. 2309
MATSUMOTO, K. 1892	MENACHEM, H. 2245*	MORRISON, J. 2112
MATSUMOTO, M. 1961*	MIAD, R. 2047	MORGAN, H.R. 2037
MATSUSHIMA, T. 1936*	MICHAEL, D. 1905*	MORI, W. 1811
MATTHEWS, N. 2222*	MICHAELIDES, M.C. 2089*	MORINAGA, N. 2026
MAUGH, T.H., II 2336*	MICHALSKI, F. 2020	MORRIS, H.P. 2123, 2306, 2331*, 2341*
MAUTNER, V. 2080*	MICHAUX, P. 1840	MORRISON, J.C. 1965*
MAVLIGIT, G. 2110, 2158	MIFTTINEN, J.S. 1862	MORRISON, W.C. 1965*
MAYER, J.B. 2144	MIKAMI, T. 2174	MORSE, P.A., JR. 2148
MCCONAHEY, W.M. 2005	MILLER, F.C. 1944*	MORTON, H.J. 2298
MCCONNELL, R.G. 1870	MILLER, G.C. 2191, 2202*	MORTON, J.I. 1951*
MCCORMICK, J.J. 1972*	MILLER, G.G. 2028	MOSER, K. 2317
MCCOY, D.W. 2295	MILLER, J.A. 1944*	MOSSES, H.L. 1985*
MCCOY, J.L. 2185	MILLER, J.M. 2183	MOTT, D.M. 1960*
MCCOY, M.G. 2125	MILLER, R.R. 1862	MOTYCKA, L. 1941*
MCCREDIE, K.G. 2110	MILLER, T. 2003	MRAZEK, R. 1957*
MCDUGALL, J.K. 2108*	MILLER, W.R. 2395*	MUELLER, S. 1884
MCDUFFIE, F.C. 2228*	MILLETTE, R.L. 1937*	MUHLBOCK, O. 2084*
MCGLASHAN, N.D. 2285*	MILLINGTON, D. 2359*	MULIVOR, R.A. 1957*
MCGREW, E. 1977*	MINDRU, I. 2261*	MULLANFY, P.F. 2004
MCINTIRE, K.R. 2151	MINOWADA, J. 2038	MULLER-BFRAT, N. 2137
MCKAY, W.S. 1948*	MINTON, J.P. 2134	MULLER, M. 2206*

MULLER, W. 2358*	NISHIO, D. 1877	ZZELLO, L. 2248
MUNRO, A.J. 2149	NISHIZUMI, M. 1956*	PAINE, A.J. 1896
MUNYON, W. 2068	NOBEL, B. 2094*	PALM, W. 2221*
MURAKAMI, T. 1831	NOBEL, T.A. 2013	PALMER, D.W. 2223*
MURPHY, G.P. 2180	NORD, S. 2192, 2203*	PALVA, T. 2163
MUSCHNER, K. 2204*	NORDIN, A. 2128	PAMUKCU, A.M. 1950*
NADKARNI, R.A. 1872	NORDQUIST, R.F. 2177	PAN, J. 2052
NAEIM, F. 2162	NOTARIO, A. 2201*	PANIGEL, M. 2096*
NAG, J. 2330*	NOVAL, J.J. 1954*	PAPAMICHAIL, M. 2219*
NAGASHIMA, Y. 2374*	NOWINSKI, R.C. 2031, 2049	PAPANIKANDROS, K. 2103*
NAGATA, C. 1835	NOYER, A.M. 2346*	PAPAS, T.S. 2075*
NAGATA, T. 2357*	NUSSBAUM, A. 2292	PAPPAS, A. 2144
NAGEL, D. 1918*	OETTGEN, H.F. 2288	PARDOE, G.I. 2303
NAHMIA, A.J. 2265	OGINO, T. 1875	PARRY, E.W. 2360*
NAIR, Z.M. 2265	O'HIGGINS, N.J. 2376*	PARSONS, J.T. 2040
NAIMY, N.K. 1910*	OKADA, M. 1830	PASSONNEAU, J.V. 2032
NAIR, B.K. 2006	OKADA, S. 1868	PASTAN, I. 2032
NAKAJIMA, T. 1881	OKAZAKI, T. 2026	PASTORE, G. 2273
NEBEL, D.T. 2352*	OLD, L.J. 2288	PATAKI, J. 1854
NEBERT, D.W. 1839	OLDSTONE, M.B.A. 2053	PATCHEFSKY, A.S. 2335*
NEKVASIL, M. 2142	OLSON, C. 2184	PATHAK, P.N. 2059
NERI, G. 2211*	OLSON, D.R. 1850	PATTENGALL, P.K. 2190
NESPOLI, L. 2140	ONOF, T. 1880	PATTERSON, E. 1905*
NEUMANN, H. 2309	ONUMA, M. 2174	PATY, D.W. 2116, 2294
NEVAR, C. 1884	ORCFL, L. 2400*	PAULISCH, R. 2130
NEWMAN, E.S. 2164	ORDER, S.E. 2253*	PAULSEN, J. 2183
NEWMAN, M.S. 1850	ORTH, G. 2062	PAVIA, R.A. 2293
NEWSON, B. 1957*	ORTIN, J. 2097*	PAYNE, L.N. 2051
NICHOLS, M. 2122	ORY, H. 2070	PAYNE, N.E. 2238*
NIEMEIER, R.W. 1984*	OSHINO, N. 2355*	PEARSON, G.R. 2055, 2065
NIEFERT, W.C. 1869	OSTER, K. 2198*	PEDICONI, M. 2299
NIITU, Y. 2374*	OTA, K. 2290	PEDIO, G. 2102*
NIKOSKELAINEN, J. 2163	OYASU, R. 1961*	PEKAREK, J. 2142
NISHIKAWA, T. 2157	OZER, H.L. 2021	PELED, A. 2045

PENNY, R. 2200*	POUND, A.W. 1827	REICHLE, F.A. 1954*
PENTA, A. 1989*	POUPON, M.F. 2178	REIF, A.E. 2195*
PENZA, R. 2121	POUR, P. 1829, 1851	REITZ, M.S. 2056
PERK, K. 2013, 2079*	POWFLL, J. 2286*	RELLA, W. 2179
PERLMANN, P. 2154	POWELL, P.C. 2051	RENNIE, M. 2051
PERONI, F. 2069	POWERS, M.L. 2171	REUTTER, W. 2124
PERZIN, K.H. 1810	PRESSMAN, D. 2038, 2160	REVELL, S.H. 1804
PETERS, L.J. 2353*	PRESTON, D.F. 2111	REVOLTELLA, R. 2299
PETERSON, A.R. 1908*	PRICE, M.R. 2167, 2230*	REYNOLDS, R.D. 2124
PETRAS, S.F. 2164	PRIFSTER, W.A. 2266, 2275	REZNIK, G. 1855
PETRICCIANI, J.C. 2182, 2295	PRIMUS, F.J. 2111	RFZNIK-SCHULLER, H. 1855
PETRU, T. 2398*	PRINGLE, J.P. 2373*	RHOADES, E.R. 2177
PETERSON, U. 2088*	PUENTES, M. 2077*	RICE, J.M. 1922*
PHILIPSON, L. 2088*	PURCHASE, H.G. 2015	RICE, J.N. 1925*
PHILLIPS, B.J. 2314	QUAGLIATA, F. 2141	RICETTI, M. 2201*
PHILLIPS, R.W. 2310	QUINTRELL, N. 2016	RICHART, R. 2070
PIECZYNSKI, W.J. 2034	RAFTELL, M. 2154	RIMAN, J. 2061
PIESSENS, W. 1996*	RAGULA, B.D. 2282*	RIMSTEN, A. 2371*
PIKE, M.C. 1814	RAINER, H. 2317	RINDE, E. 1927*
PILIPENCO, N.N. 1879	RAINERI, R. 1938*	RISCA, R. 2313
PINCUS, T. 2076*	RAJEWSKY, M.F. 1865	ROBERSON, D.L. 2350*
PIPER, P.W. 2315	RAJU, M.R. 2004	ROBERTS, M.M. 2233*, 2344*
PIROFSKY, R. 2215*	RAMASAMY, R. 2149	ROBERTSON, S. 2173
PLANT, A.F. 2008	RAMIREZ, G. 1952*	ROBINSON, J.R. 1839
PLATA, E.J. 2158	RAN, M. 2127	ROBSON, R.T. 2238*
PLATA, F. 2197*	RANDERIA, J.D. 1993*	RODRIGUES, D. 2187
POIRIER, L.A. 1948*	RASMUSSEN, R.E. 1915*	ROEBUCK, B.D. 1943*
POIRTER, M.C. 1940*	RASTETTER, J. 2137	ROIZMAN, B. 2109*
POLAN, A.K. 2249	RAVRY, M. 2151	ROLLINGHOFF, M. 2214*
POLAND, A.P. 1839	RAWLINSON, D.G. 2334*	ROMERO, A. 2004
POLJAK, R.J. 2217*	RAWLS, W.E. 2064	ROSENBERG, I.H. 2309
POLLARD, M. 2128	RAYMAN, M.P. 1982*, 1992*	ROSS, K.B. 2093*
POPP, J.A. 1901*	REDDY, C.R.R.M. 2271	ROTHMAN, B. 2146
POSTE, G. 2035	REEVE, P. 2035	ROTHWELL, K. 1885

ROWLAND, R.E.	SCHARFF, M.D.	SHAH, I.C.
2002	2131	2003
ROWLATT, C.	SCHECHTMAN, L.M.	SHAMBERGER, R.J.
2397*	1929*	1921*
RUBINSTEIN, L.J.	SCHIEDTMANN, K.M.	SHANMUGARATNAM, K.
2334*	2097*	2150
RUBIN, C.A.	SCHIEINMAN, H.Z.	SHANTZ, G.D.
2258*	2319*	2186
RUDALI, G.	SCHERKOLODKIN, V.F.	SHAPIRO, S.
1997*	2339*	1852
RUDDLE, F.H.	SCHENKER, L.	SHARMA, J.M.
2297	2296	2015
RUDOLPH, R.	SCHERLERN, P.G.	SHARMA, U.
2183	2144	1952*
RUITENBEK, A.	SCHICHA, H.	SHATTON, J.B.
2218*	2358*	2305
RULE, A.H.	SCHLESINGER, S.	SHAUFFER, I.A.
2170	2089*	2195*
RUNDT, J.	SCHMIDT, C.G.	SHAYMAN, M.A.
2002	2316	1942*
RUNTAAR, B.A.	SCHMIDT, N.J.	SHEARMAN, D.J.C.
2218*	2175	1826*
RUSSELL, R.M.	SCHNEIDER I.	SHEEHY, P.F.
2309	2091*	2278
RUTHERFORD, R.B.	SCHNEIDER, I.	SHELDON, P.
2019	2091*	2219*
RYAN, W.L.	SCHOENTAL, R.	SHFLINE, G.E.
1924*	1991*	2005
RYMO, L.	SCHONLAND, M.	SHENEFELT, R.E.
2040	2269	1922*
SACHS, L.	SCHREML, W.	SHEPHEARD, B.G.F.
2301	2368*	2118
SADDUGH, N.	SCHRODER, R.	SHERBET, G.V.
2196*	2358*	2302
SAHAKIAN, G.J.	SCHUIT, H.R.E.	SHERIFF, M.U.
2381*	2129	2397*
SAIDONTZ, H.	SCHULTE-HERMANN, R.	SHIH, M.
2324*	1806	2018
SALIH, H.	SCHUTT, A.J.	SHIMADOKA, K.
2377*	2151	2012*
SALIM, I.	SCHWARTZ, J.P.	SHIMIZU, H.
2354*	2032	1918*
SALUJA, M.	SCHWIFIZER, K.	SHIMJUN, H.
2296	2135	2057
SALUJA, P.G.	SCHWIND, J.V.	SHIMOSATO, Y.
1995*	1821*	2321*
SANCHEZ DE CALVOJA, L.E.	SCRIBNER, J.D.	SHIN, T.W.
2254*	1910*	1914*
SANI, B.P.	SEEBER, S.	SHINDZUKA, H.
1960*	2316	1901*
SAPOZINK, M.	SEGALL, A.	SHIRADABE, H.
1932*	2245*	1831
SARIN, P.S.	SEGALOFF, A.	SHIROKI, K.
2056	1894	2057
SARMA, D.S.R.	SEIBERT, K.	SHIU, G.
1967*	2128	2187
SASADATRA, S.	SELL, S.	SHIVAS, A.A.
2321*	2122, 2123, 2124	2395*
SAUERMANN, G.	SEPP, F.	SHOHAM, J.
2349*	2137	2301
SCHACHTSCHABEL, D.	SEREPROV, A.I.	SHOHAT, B.
2362*	1813	2216*
SCHAEFFER, B.	SERNKA, T.J.	SHUBIK, P.
2035	2364*	1832
SCHAFER, W.	SESSIONS, R.B.	SHUPACK, J.
2091*	2064	2207*
SCHANKE, D.A.	SEVOIAN, M.	SIEGEL, B.V.
1898	2042	1951*

SILFVERSWARD, C. 2380*	SILG, W.G.S. 2234*	STREIT, I. 2317
SILVERNAIL, P. 2292	SPRINGER, G.F. 2212*	STRNAD, M. 2264
SIMONS, M.J. 2150	SRAM, R.J. 1863	STUBBS, M. 2355*
SIMPSON, M. 1949*	SRETER, L. 2338*	STUCIN, M. 2260*
SIMS, P. 1971*	SRIVASTAVA, B.I.S. 2312	SUAREZ-ALVARADO, M. 2240*
SINCLAIR, T.F. 1917*	STACHER, A. 2317	SUBRAMANIAN, K.N. 2052
SINDRAM, I.S. 1994*	STANKLER, L. 2329*	SUETAKE, T. 2374*
SIRMAKECHTAN, K. 2103*	STANLEY, E.M. 2236*	SUGAI, S. 2223*
SIVAK, A. 1969*	STASZEWSKI, J. 2272	SUGAYA, T. 1892
SJOGREN, H.H. 2208*	STATHOPOULOS, G. 2219*	SUGIHARA, S. 1877
SJOGREN, H.D. 2138	STAUFFER, R.D. 1902*	SUGIMURA, T. 1851, 1936*
SKIBBA, J.L. 1945*	STAVROU, D. 1874	SUGIYAMA, T. 1875
SKINNER, G.R.B. 2104*, 2283*	STEELE, G., JR. 2138	SUMIDA, M. 1831
SLAGA, T.J. 1925*	STEER, A. 2274	SUNDERMAN, F.W. 1895
SLONE, D. 1862	STEGNER, H.E. 2259*	SUPRAPTO 2354*
SMETS, L.A. 2304	STEIN, H. 2145	SUSS, R. 1887
SMITH, D.F. 2211*	STEFNER, S. 2029	SUZUKI, H. 2322*
SMITH, G.C. 2095*, 2096*	STEINKAMP, A. 2004	SUZUKI, K. 1830
SMITH, G.S. 2162	STENBACK, F. 1832, 1924*	SWANN, P.F. 1990*
SMITH, H.G. 2159	STEPHENSON, J.R. 2030, 2090*	SWEDO, J.L. 2106*
SMITH, P.G. 1814	STEVENS, N. 1860	SWENSON, D.H. 1944*
SMITH, R.E. 2060	STEWART, A.M. 2169	SWITZER, P. 2277
SMITH, S.R. 2171	STICH, H.F. 2058	SYDNOR, K.L. 1959*
SOBHY, C.M. 1965*	STICH, W. 2058	SZYBALSKI, E.H. 1946*
SOBIS, H. 2361*	STIMPFLING, J. 2098*	TABUCHI, Y. 1875
SOEHNLEN, B. 2117	STODDARD, A. 2162	TAGASHIRA, Y. 1835
SOKAL, J.E. 2012*	STONER, R.D. 2115	TAKAGI, M. 1811
SOKOLVA, I.S. 1879	STORR, R. 2132	TAKAHASHI, G. 1899
SODHOO, J. 2279	STOTZ, G. 2338*	TAKAHASHI, H. 1853
SORTANO, R.Z. 2348*	STOWELL, R.E. 1934*	TAKAYAMA, S. 1851
SOROF, S. 1960*	STOWELL, R.E., JR. 1934*	TAKEDA, M. 2335*, 2348*
SPARKS, H.A. 2352*	STRAND, M. 2076*	TAKEUCHI, T. 1935*
SPELSBERG, T.C. 1985*	STRAUSSER, H.R. 2017	TALAL, N. 2223*
SPIEGEL, H.E. 2342*	STREBEL, J. 2137	TALLEY, R.W. 2106*

TANAKA A.	TING, R.C.	TYAN, M.L.
1881	2072	2194*
TANAKA, H.	TISDALE, M.J.	UCHIDA, S.
2067	2314	2036
TANAKA, N.	TKADLECEK, L.	UGAROVA, T.Y.
1851	2337*	1879
TAPER, H.S.	TODORUTIU, C.	UGAZIO, A.G.
1841	2313	2140
TARTVE, G.	TOFT, D.O.	ULRICH, J.
2069	1963*	2328*
TASSI, G.C.	TOH, B.H.	UMEZAWA, H.
2225*	2155	1936*
TAURELLE, R.	TOJYO, K.-I.	UNGUREANU, M.
2325*	1881	2261*
TAWASHY, K.	TOKUNAGA, A.	URBACK, F.
2347*	1851	1966*
TAYLOR, A.M.R.	TOMATIS, L.	VALENTINE, F.T.
2383*	1842	2288
TAYLOR, C.W.	TOMPKINS, E.A.	VALSAMIS, M.
1913*	2005	2324*
TAYLOR, D.M.	TONDER, O.	VAN DE VOORDE, A.
2001	2148	2092*
TAYLOR, M.W.	TORGENSEN, O.	VANDEPUITE, M.
2074*	1882	2361*
TAYLOR-PAPADIMITRIU, J.	TORTORA, M.	VANDERLAAN, M.
2103*	2105*	1969*
TEGTMAYER, H.	TOTH, B.	VARMUS, H.E.
2212*	1918*	2016
TELFORD, J.	TRABER, J.	VASILJEVA, V.A.
2395*	2340*	2339*
TEPPD, L.	TRAININ, N.	VEIT, R.
2262	2193*	2014
TERAMOTO, Y.	TREVES, A.J.	VELLIS, F.
2077*	2193*	1975*
TERENIUS, L.	TROLL, W.	VESSELINOVITCH, S.D.
2371*	1927*	1979*
TERRACINI, B.	TRONICK, S.R.	VESSEY, M.P.
2273	2030, 2090*	1852
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1859	2365*	2069
THOMAS, C.F.	TRUJILLO, T.T.	VIRASORO, S.
2234*	2004	2112
THOMAS, L.	TSAKRAKLIDES, E.	VOGT, P.K.
2288	2139	2044
THOMPkins, W.A.F.	TSAKRAKLIDES, V.	VOLCKAERT, G.
2059	2139	2092*
THOMPSON, D.L.	TSAN, M.C.	VOOIJIS, P.G.
1948*	2293	1994*
THOMPSON, J.F.	TS'IO, P.O.P.	VORBECK, M.L.
2318	1929*	2331*
THOMPSON, S.	TSO, T.C.	VOSE, C.W.
1925*	1926*	1970*
THOMPSON, S.C.	TSOI, M.S.	VRBA, M.
2323*	2132	2291
THORBECK, G.J.	TSOU, K.C.	WAHLEN, W.
2190	2125	2144
THORELL, B.	TSUANG, J.	WAKONIG-VAARTAJA, T.
2362*	1958*	2278
THOREN, L.	TSUCHIDA, N.	WALBORG, E.F., JR.
2371*	2018	2211*
THORNTON, J.	TSUJIMURA, D.	WALBURG, H.E., JR.
1975*	2067	1818
TI, T.K.	TSUTSUI, Y.	WALDMANN, T.A.
2150	1845	2151
TING, C.C.	TURUSOV, V.	WALFORD, R.L.
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WALKER, S.A. 1834	WEISS, R.A. 2099*	YAMAGJCHI, K. 2057
WALLACE, R.E. 2295	WEISSMAN, I.L. 2192, 2203*	YAMAGUCHI, N. 1955*
WALTERS, R.A. 2004	WEISSMAN, S.M. 2052	YAMAKAWA, T. 2393*
WANG, C.Y. 1952*	WEISSMANN, C. 2040	YAMAMOTO, R.S. 1936*
WANG, I.Y. 1911*	WELLS, M. 2172	YANG, S.S. 2072
WANG, S. 2074*	WENK, M.L. 1948*	YASUI, A. 1831
WARD, J.M. 1900*	WHEATLEY, D.N. 2101*	YEH, S. 1838
WARD, S.P. 2345*	WHITEHEAD, R.H. 2235*	YEOMAN, L.C. 1913*
WARNER, M.R. 1988*	WHITFIELD, J.F. 2298	YERGANIAN, G. 1989*
WARNER, R.L. 1988*	WHUR, P. 2238*	YESNER, R. 2277
WASHBURN, L.L. 1916*	WHYBREW, W.D. 1965*	YONG, N.K. 2150
WATANABE, T. 2000	WIGLEY, C.B. 1981*	YOSHIDA, Y. 1880
WATANABE, Y. 2047	WILLCOX, H. 2080*	YOSHIIKE, K. 2036
WATNE, A.L. 1949*	WILLFMS, G. 1802	YOSHIKI, T. 2076*
WATSON, D.W. 2113	WILLIAMS, S. 1847	YOST, Y. 1912*
WATSON, J.H.L. 2106*	WILLIAMS, W.H. 2191	YOUNG, B.G. 2050
WAWRZKIEWICZ, M. 2398*	WILLIS, C.E. 1921*	YUSPA, S.H. 1935*
WEBER, G. 2341*	WILSON, D.F. 2355*	YUTOKU, M. 2160
WEBER, K. 2041	WILSON, R.G. 2344*	ZABIELSKI, J. 2078*
WEBER, T. 1889	WILTSHAW, E. 2219*	ZAHARIA, M. 2375*
WECHSLER, B. 2245*	WINN, R. 2278	ZAIN, S. 2052
WEF, G.B. 2150	WISER, W.L. 1965*	ZAMCHECK, N. 2169
WEHRLY, K. 2098*	WITZ, I.P. 2127, 2223*	ZAMECHNIK, P.C. 2168
WEIDEN, P.L. 2132	WOGAN, S.N. 1943*	ZANG, K.D. 1874
WEIG, J. 2137	WONG, S.H. 2150	ZANKL, H. 1874
WEIL, R. 2078*	WOOD, B.G. 1916*	ZECH, L. 2289
WEINBERG, R. 2021	WORKMAN, J.B. 2005	ZEDECK, M.S. 1932*
WEINHOUSE, S. 2306	WORTZMAN, G. 2346*	ZETTERBERG, A. 2379*, 2380*
WEINSTEIN, I.R. 1955*, 1976*	WRBA, H. 2284*	ZHDANOV, V.M. 2023
WEISBURGER, E.K. 1900*	WYLLIE, A.H. 2305	ZIFGLER, J.R. 2200*
WEISBURGER, J.H. 1938*	WYNDER, E.L. 1958*	ZIMBER, A. 2013
WEISGRAS, J.M. 1976*	YAGI, M.J. 2081*	ZIMOLN, A. 2264
WEISINGER, E. 2382*	YAKOVLEVA, L.A. 2339*	ZIZMOR, J. 2346*
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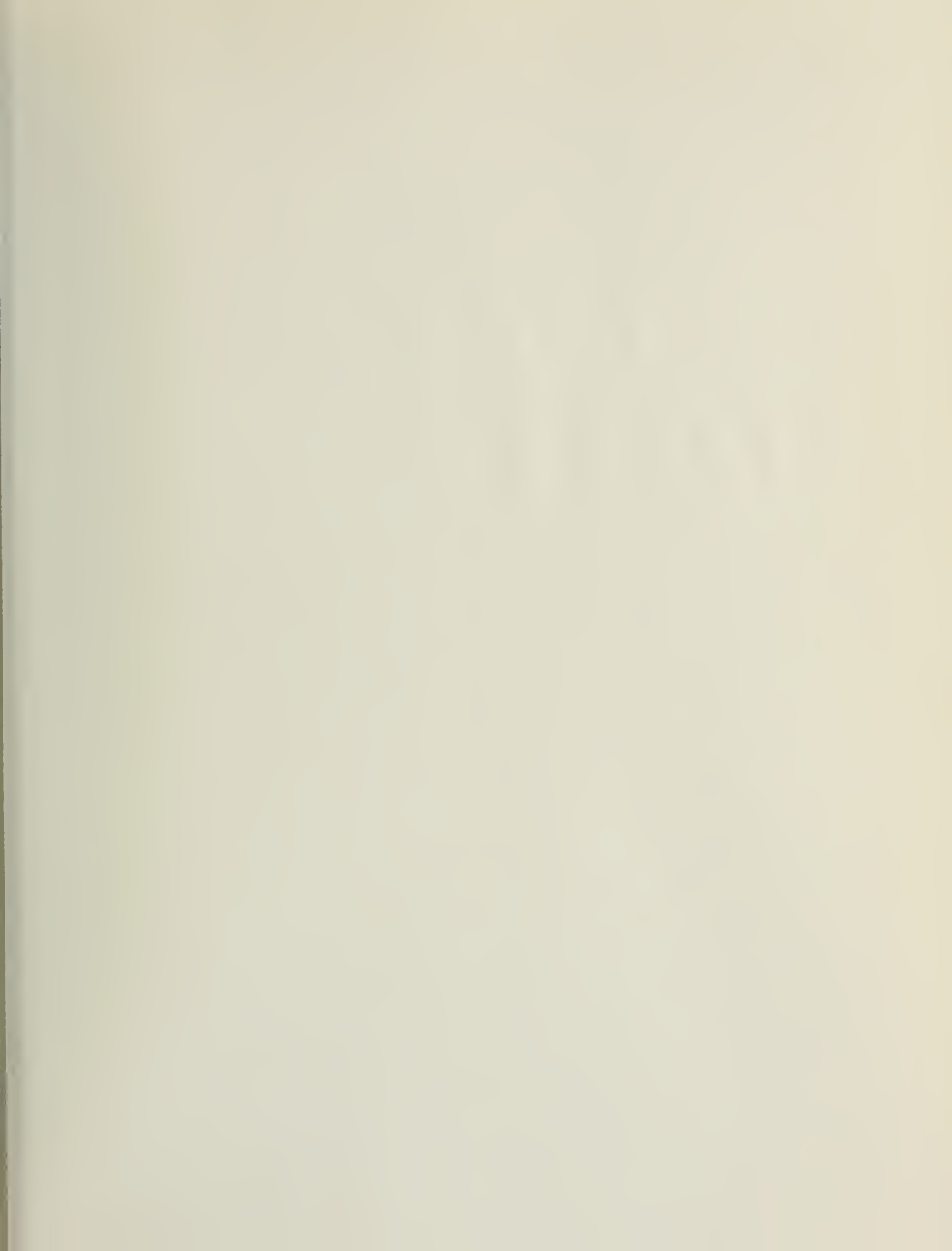
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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
In.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	RNA	ribonucleic acid
i.m.	intramuscular	s.c.	subcutaneous
i.p.	intraperitoneal	sec	second(s)
IU	international unit(s)	U	unit(s)
i.v.	intravenous	UV	ultraviolet
kg	kilogram(s)	WBC	white blood cells (leukocytes), white blood count
LD ₅₀	median lethal dose(s)	wk	week(s)
m	meter(s)	wt	weight(s)
M	molar	yr	year(s)
mEq	milliequivalent(s)		
mM	millimolar		
µM	micromolar		
mC, µC	milli-, microcurie(s)		

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2401 THE DIFFERENTIATION AND ORGANIZATION OF TUMORS *IN VITRO*. (E.) Auersperg, N.

(Cancer Res. Ctr., U. British Columbia, Vancouver, Canada) and C. V. Finnegan. *Neoplasia and Cell Differentiation*, Basel, Karger:279-318, 1974.

The effects of the tissue culture environment on explanted normal tissues and on tumor tissues are compared with reference to the culture of normal tissues, the organ culture, matrix culture, and short- and long-term cell-layer culture of explanted tumors, and malignant transformation *in vitro*. Specific topics include: histotypic organization in long-term tumor cultures, differentiation in long-term tumor cell lines and suspension cultures of tumor cell lines. Malignant transformation *in vitro* in terms of changes in cellular morphology and behavior is discussed with regards to the contact inhibition of movement, the density-dependent inhibition of growth, the dependence of changes in cellular morphology and behavior on substrata and growth factors, differentiation of transformed cells, cellular morphology, and the structural basis for cellular changes. (204 references)

2402 ARENE OXIDES: A NEW ASPECT OF DRUG METABOLISM. (E.) Jerina, D. M. (Natl. Inst.

Arthritis, Metab., Dig., Dis., Bethesda, Md.) and J. W. Daly. *Science* 185(4151):573-582, 1974.

Arene oxides have been identified as intermediates in the metabolic formation of phenols, trans-dihydrodiols, and premercapturic acids in mammals. The steady-state concentrations of intermediate arene oxides are related to the rates at which they are formed, their ability to isomerize to phenols, to react with nucleophiles such as glutathione, and to undergo enzymatic hydration. The covalent binding of these bioactivated intermediates to intracellular macromolecules provides a molecular basis for the cytotoxicity of aromatic hydrocarbons and the carcinogenicity of polycyclic hydrocarbons. The nature of the sites of binding to biopolymers, and the complex set of kinetic and structural parameters that influence both the reactivity of arene oxides and their ability to bind to critical target molecules are under investigation; however, such factors have not been completely defined for any aromatic hydrocarbon. That bioactivated intermediates other than arene oxides also have a role in the carcinogenicity of polycyclic hydrocarbons remains a possibility. (109 references)

2403 SOME ASPECTS OF THE IMMUNOLOGY OF HODGKIN'S DISEASE. (E.) Crowther, D. (St. Bartholomew's Hosp., London, England). *Tumor* 59:351-362, 1973.

Although Hodgkin's disease patients are particularly liable to developed depression of cell-mediated immunity, antibody formation to most antigens is normal until the disease is well advanced. There is no evidence of an impaired phagocytic function of the reticuloendothelial system (RES) in Hodgkin's disease, but there is considerable evidence of qualitative and quantitative abnormality in lymphocyte function. A

reduction in the number of circulating small lymphocytes correlated with a reduction in delayed hypersensitivity responses is a feature of advanced Hodgkin's disease. Increased periodic acid-Schiff (PAS) staining has been found in lymphocytes from patients with untreated Hodgkin's disease, these lymphocytes also being unable to transform into large proliferating lymphoid cells in response to phytohemagglutinin, antigens to which they have been sensitized, or contact with allogeneic cells or antibody directed against membrane antigens of the lymphocyte. The evidence indicates that the main cause of the immunosuppression in Hodgkin's disease may be due to quantitative and qualitative defects in the thymic dependent small lymphocytes. The peripheral blood lymphoid population in Hodgkin's disease differs from normal in an increased number of large lymphoid cells actively synthesizing DNA, an increased number of medium sized lymphoid cells with intensively basophilic cytoplasm, and the presence of occasional plasma cells. Although these changes are compatible with an immune reaction, the antigen against which the reaction is directed is not known. Similarly, while there is a good correlation between the degree of lymphoid cell reactions and prognosis, there is no strong evidence of causative relationship between these two factors. Preliminary evidence of a tumor-associated antigen in Hodgkin's disease has been obtained, although the tumor-associated antigens have not been shown to be specific for the tumor cell in Hodgkin's disease. Blast transformation has been observed when small lymphocytes from Hodgkin's disease patients are cultured *in vitro* in the presence of an autologous lymph node homogenate. The immunological abnormalities support the hypothesis that a graft-versus-host reaction plays an important part in the pathogenesis of Hodgkin's disease. (35 references)

2404 CYCLIC AMP, PROSTAGLANDINS, AND THE CONTROL OF CELL PROLIFERATION. (E.) MacManus, J.

P. (Div. Biol. Sci., Natl. Res. Council Canada, Ottawa, Ontario) and J. F. Whitfield. *Prostaglandins* 6(6):475-487, 1974.

The evanescent changes in cyclic-AMP levels which occur in cells which are actively cycling in a synchronous or semi-synchronous manner are reviewed. The doses of prostaglandins PGE₁ and PGA₁ which stimulate adenylate cyclase and increase cyclic-AMP levels also stimulate cell proliferation. Exogenous cyclic-AMP is able to mimic the mitogenic action of the prostaglandins, as shown by its ability to initiate DNA synthesis. These stimulated cells, like those treated with PGE₁, enter mitosis 3-4 hr after treatment. Cyclic-AMP also stimulates cell proliferation in the rat thymus *in vivo*. When calcium is present in the culture medium *in vitro*, PGE₁ can increase cyclic-AMP levels and stimulate DNA synthesis, but the stimulated cells cannot enter mitosis unless the calcium is removed. *In vivo*, a biphasic increase in cyclic-AMP occurs following 70% hepatectomy, with peaks at 2.5 and 12 hours, followed by the initiation of DNA synthesis at 16-18 hours. Adrenergic blocking agents given immediately after surgery eliminate the first peak, but do not interfere with the second peak or the initiation of DNA synthesis. Given 8 hours

after surgery, they decrease and delay the cyclic-AMP response and the initiation of DNA synthesis. These drugs do not affect ongoing DNA synthesis. The infusion of a mixture of thyroxine, amino acids, glucagon, and heparin for 3 hours into intact rats causes two peaks of cyclic-AMP accumulation, similar to those following partial hepatectomy; these changes are followed by the initiation of DNA synthesis, which peaks at 21-22 hours. Thus, an increase in the cyclic-AMP concentration occurs as cells enter the cell cycle, this increase being related to the initiation of DNA synthesis. (17 references)

- 2405 IMMUNOLOGICAL STUDIES IN BREAST CANCER.
(E.) Lentino, J. A. (USAGH, Frankfurt, W. Germany). *Med Bull US Army Eur* 31(9):268-272, 1974.

The radial immunodiffusion technique was used to determine the IgA, IgM, IgG, and C₃ levels in the sera of 123 females with benign breast disease, 24 females with breast cancer, and 33 healthy female controls. Compared with the controls, the IgM levels were significantly elevated in the breast cancer sera. IgM was also significantly higher in cancer patients in Stage I compared with those in Stage II. IgG was also significantly elevated in Stage I compared with Stage II, and in patients with metastases to the axillary lymph nodes. An inverse association between sinus histiocytosis and node metastases was indicated. IgM values were also elevated in the patients with benign breast disease, most of whom had fibrocystic disease. The data support the view that immunological phenomena play a significant role in the biological behavior of breast cancer. (41 references)

- 2406 HUMAN GENETIC MARKERS AS TRACERS OF TUMOUR HISTOGENESIS. (E.) Fialkow, P. J. (Dept. Med., U. Washington, Seattle). *J Clin Pathol [Suppl]* 27(7):11-15, 1974.

The glucose-6-phosphate dehydrogenase (G-6-PD) marker system has been successfully employed to investigate the development of several human tumors. However, the etiologies of most human tumors which have been studied are unknown. If X-linked genetic marker studies could be done in tumors with known etiology, the results might have implications for neoplasms of unknown cause. This approach is currently limited by the small number of human neoplasms for which an etiological agent has been defined, and by inability to detect markers at the cellular levels for X-linked loci with frequently occurring variant alleles other than G-6-PD. Until more markers are discovered, continued investigation into human tumors with X-linked markers will be essentially confined to black populations. In addition to further studies of hereditary tumors, warts, and Burkitt lymphoma, it should be profitable to include other tumors which arise under more or less defined circumstances, such as those associated with radiation exposure, organic chemicals, and endocrine and immunological changes. Once suitable X-linked markers are discovered in lower organisms, direct studies can be undertaken. Hopefully, information gained from subhuman primate studies would have a bearing on the causes of human malignancies. (30 references)

- 2407 SEARCH FOR A VIRAL ETIOLOGY OF HUMAN BREAST CANCER. (E.) Lasfargues, E. V. (Inst. Med. Res., Camden, N.J.) and D. H. Moore. *J Invest Dermatol* 63(1):125-132, 1974.

The authors briefly review the steps to the understanding of mouse mammary carcinogenesis and its application to the available human data; the viral hypothesis for breast carcinogenesis in man is discussed. A virus (murine mammary tumor virus, MTV) produced at the cell membrane of mammary epithelial cells can cause mammary tumors in mice. This virus is infective, has spikes on its external membrane, a nucleoid which contains a reverse transcriptase, and a high-molecular-weight RNA. There is no evidence of a similar virus particle budding from the epithelial cells of human breast tumors; however, virus-like structures have been found in human milk and in tissue culture supernatant fractions of human tumor cells. These structures are comparable to the virus-like particles found in the milk of breast cancer patients and are morphologically similar to the murine viruses. Despite the lack of budding viruses in the primary breast tumor cell cultures, biochemical evidence of a reverse transcriptase and a high-molecular-weight (70 S) RNA in these cultures could indicate virus reproduction. Human antibodies from the sera of breast cancer patients will neutralize the antigen localized on the outer membrane of mouse mammary tumor cells. These observations strongly suggest the existence of a human breast cancer virus which has not yet been characterized. (24 references)

- 2408 EFFECTS OF TUMOUR VIRUSES ON CELL GROWTH.
(E.) Stoker, M. G. P. (Imperial Cancer Res. Fund Labs., London, England). *J Clin Pathol [Suppl]* 27(7):60-64, 1974.

Physiological factors which determine whether a cell will remain in the G₀ state (inhibited state probably representing an alternative "holding" regulation state) or continue the growth cycle in G₁ (the whole cycle of growth) include the general environment and the local environment of a particular cell. General factors influencing cell growth are nutritional deficiencies, proteases, and, in theory, negative feedback through the accumulation of inhibitors in the medium. Local factors influencing cell growth include anchorage to a surface on which the cell can spread and cell-to-cell contact. The cell membrane may mediate this growth control system which responds to environmental signals. The general effect of tumor viruses is to make cells unresponsive to their environment; they stimulate cell to grow under conditions which normally maintain the cells in G₀. The abnormal growth is probably due to virus-specified proteins. Other changes in the structure and function of cell components affected by tumor viruses include increased agglutinability by lectins, stimulated transport of several small molecules, and general changes in the surface chemistry affecting glycopeptides and glycolipids. There are important differences between the two main groups of viruses, the DNA tumor viruses and the leucoviruses: the latter, but not the former, can replicate without simultaneously killing cells; and abnormal growth is not an essential requirement for replication of the leucoviruses,

while the multiplication of the DNA viruses and stimulation of the cell cycle are nearly always associated. Leucoviruses can probably also affect different targets than DNA tumor viruses. (22 references)

- 2409 EPIDEMIOLOGY OF HUMAN BREAST CANCER. (E.)
Cole, P. (Dept. Epidemiol., Harvard Sch.
Public Hlth., Boston, Mass.). *J Invest Dermatol*
63(1):133-137, 1974.

A descriptive and analytic epidemiology of breast cancer is reviewed. Race, religion, socioeconomic status, age at menarche, age at first birth, lactation, parity, artificial menopause, age at natural menopause, weight, previous breast disease, and family history are all related to the epidemiology of human mammary cancer. Lactation is not protective against breast cancer, while multiparity is associated with low breast cancer in a noncausal way. The association with parity results from the fact that both high parity and low breast cancer risk are associated with an early age at first birth. The major causal hypotheses relating to breast cancer fall into genetic, viral, and endocrine categories. The genetic hypothesis is supported only by the existence of familial aggregation, while viral involvement in the human disease is only weakly supported by laboratory and population studies. However, both laboratory and population data strongly support an endocrine etiology of breast cancer. The four major endocrine hypotheses relate to progesterone, prolactin, androgens, and estrogens, and recently prolactin has become a major contender. With regard to the estrogens, the estriol ratio which characterizes a woman's young adulthood may be a determining factor in her risk of breast cancer. The urinary estrogen profiles were compared in young women from two North American cities (high breast cancer rates) and three areas in Asia (relatively low breast cancer rates). The data support the estrogen hypothesis. (33 references)

- 2410 THE ROLE OF CIRCULATING ANTIBODY IN THE
CONTROL OF METASTASES. (E.) Lewis, M. G.
(McGill U. Cancer Res. Unit, Montreal, Canada). *J Clin Pathol [Suppl]* 27(7):83-93, 1974.

The role of circulating antibody in the control of metastases is reviewed. Antibody against components of tumor cells has been reported in a number of human malignancies, notably malignant melanoma, and in several animal models. The neoplastic cell contains numerous potential antigens, including cell surface antigens, cytoplasmic antigens, and antigens in the nuclear and nucleolar structures. The antibody/antigen reaction takes place against a component of the tumor and not against components of normal tissue, thus establishing tumor specificity. There is evidence that antibody/antigen reactions in patients with malignancy can be either beneficial or detrimental depending on the timing, the type of antibody, and the antigen concerned. Possible mechanisms for loss of circulating antibodies in malignancy and metastatic spread of tumor are a lack of responsiveness on the part of the host; an alteration in the

immunogenicity of the tumor; effective neutralization of the antibody by a rapidly developing tumor; and the existence of a serum substance which could block the effectiveness of circulating antibody against tumor cells. The latter mechanism is the most plausible in view of experimental evidence. There is some indication that slowly forming complexes between tumor-specific antibody and some tumor antigens result in deposition of antibody-antigen complexes in the basement membrane of the kidney, with subsequent damage and the production of a progressive nephrotic syndrome. It is possible that antibodies could be produced against components of the tumor cell which do not have a primarily protective function but are dependent on other immune processes; the antibody cytoplasmic components might well be considered under such a heading. (65 references)

- 2411 THE ROLE OF MACROPHAGES IN TUMOUR IMMUNITY.
(E.) Alexander, P. (Chester Beatty Res.
Inst., Sutton, Surrey, England). *J Clin Pathol [Suppl]* 27(7):77-82, 1974.

The term "arming" is used to describe the process by which macrophages acquire *in vitro* the capacity to inhibit the growth and/or kill target cells in an immunologically specific manner. The growth inhibitory action of macrophages from suitably immunized animals or "armed" *in vitro* can be directed against the normal transplantation antigen of the tumor cells or in syngeneic systems against the tumor-specific antigens. Such macrophages exert their action by membrane contact with the target cell. Immune or armed macrophages become "activated" following incubation with the specific antigen, i.e., they acquire the ability to inhibit *in vitro* the growth of a variety of sarcoma and lymphoma cells. Transformation from an armed to an activated state by contact with specific antigen also occurs *in vivo*; in the absence of further antigen, however, macrophages lose their activation. In mice, a persistent infection will cause macrophages to become armed and to remain activated. Macrophages can also be activated *in vivo* and *in vitro* by exposure to endotoxin Bacille Calmette-Guerin, or double-stranded RNA. There is evidence that macrophages are involved in the rejection of tumor cells injected i.p. into immunized mice, in the reaction of the syngeneic host to solid tumors, and in the phenomenon of concomitant immunity to metastatic spread. The phenomenon of activating macrophages in mice immunized against an antigen totally unrelated to tumors can be exploited for immunotherapy. The practical usefulness of such treatments is limited, however, because macrophage activation is largely confined to the site into which the antigen has been injected. (18 references)

- 2412 OBSERVATIONS ON THE GENESIS OF HUMAN LEUKEMIAS. (Ger.) Mey, U. (Med. Clin., Med.
Acad., Erfurt, Germany). *Z Gesamte Inn Med* 29(14):
559-563, 1974.

Although leukemias are conventionally classified as lymphatic or myeloid, the classification system of Bessis takes into account neoplastic proliferation

of all systems of blood cells. While epidemiological studies suggest that endogenous risk factors are generally the most important in childhood leukemia, exogenous factors (ionizing radiation, viral and bacterial infections, and allergic diseases) may also play a role *in utero*. Certain chemicals (benzene) and drugs (chloramphenicol, phenylbutazone, and cytostatic agents) have been implicated as potential leukemogenic agents, but the extent to which a cause-and-effect relationship has been established differs. In animals, virus-induced leukemias and lymphomas, some of which are analogous to those observed in man, are caused by RNA viruses which may remain latent for long periods before they induce cell transformation. This long latent period can be explained by Killmann's stem cell theory, according to which leukemia probably develops in dormant sleeper cells (pluripotent stem cells). These sleeper cells are normally differentiated into feeder cells (differentiated stem cells), but localized disturbances in differentiation can result in the accumulation of pathologically changed cells in different states of maturity. This theory is supported by detection of the Philadelphia chromosome in granulocytes, erythropoietic cells, and megakaryocytes in chronic myeloid leukemia. The conversion of sleeper cells into feeder cells can be speeded up by removal of blood. In this way, the incidence of leukemia was increased from 4% to 100% in RF mice; similar results were obtained in irradiated rats. (30 references)

- 2413 THE MALIGNANT CELL AND ITS MEMBRANES. (E.) Warren, L. (U. Pennsylvania Sch. Med., Philadelphia). *Am J Pathol* 77(1):69-76, 1974.

The hypothesis that altered membrane proteins and glycoproteins may be critical mediators of malignant expression is discussed. The mutation or virus infection leading to malignancy probably leads to the production of altered proteins, possibly a critical membrane enzyme. An alteration in a membrane protein might alter the kinetic characteristics of enzymes and their response to metabolites, thus leading to further structural or metabolic changes. Upon transformation, a band of high molecular wt material, probably a glycoprotein, is decreased or eliminated from the surface structure of the cell. The carbohydrate component of membrane glycoproteins has been compared using the double-label method. A peak of glycopeptides, peak A, is present in transformed cells but is present in only small quantities as a shoulder in nontransformed cells. After neuraminidase treatment, the patterns of the two cells become identical. The production of Peak A glycopeptides is growth dependent, not occurring in cells which have ceased to divide. An enlarged peak A is seen in cells from a variety of species and transformed spontaneously, chemically, or by DNA or RNA oncogenic viruses. The peak A pattern is a generalized change taking place in the glycoproteins of all the membrane systems of the cell. Peak A glycopeptides bearing "extra" sialic acid residues may be accounted for by a sialyl transferase that is present in greater amounts in transformed cells than in control cells; the enzyme is membrane-bound. Peaks A and B are different, representing two independent families of

glycopeptides. It is probable that the sialyl transferase is only one of several sugar transferases responsible for the formation of peak A glycopeptides of glycoproteins that is elevated during malignancy. (21 references)

- 2414 CANCER OF THE GASTROINTESTINAL TRACT: HISTOGENESIS AND PREMALIGNANT LESIONS. (E.) Ming, S. C. (Temple U. Med. Sch., Philadelphia, Pa.). *JAMA* 228(7):886-888, 1974.

Histologically, the development of gastric carcinoma involves three fundamental problems: the cellular origins of cancer cells, the developmental sequences of cancer, and the premalignant conditions. It is likely that the cancer cells develop from poorly differentiated mucus-producing cells. The cells of the gastric mucosa adjacent to a carcinoma may be categorized in order of increasing potential for malignant transformation: simple hyperplastic cells, atypical hyperplastic cells, and anaplastic cells. These cell-forms probably represent histogenetic stages of malignant transformation. There are two types of premalignant lesions: for a truly premalignant lesion the emphasis should be on the lesion itself; in conditions with a high incidence of co-existing malignancy, the emphasis should be on the gastric mucosa outside the lesion. Villous adenoma may be considered premalignant in the first sense, while chronic peptic ulcer, chronic atrophic gastritis, mucosal atrophy, intestinal metaplasia, hyperplastic gastropathy, and hiatal hernia may be considered premalignant only in terms of their more frequent association with carcinomas than normal mucosa. Whenever these abnormalities are present, the gastric mucosa should be examined carefully for carcinoma. (14 references)

- 2415 CANCER IMMUNOLOGY. (Fr.) Burtin, P. (Inst. Sci. Res. Cancer, Villejuif, France). *Bull Acad Natl Med* 157(7):545-548, 1974.

The principal tumor antigens are located on the membrane of tumor cells. They have either been observed by the fluorescent antibody method or postulated where conditions warrant it. The nature of the antigens depends on the origin of the tumor: for tumors caused by a given virus, all tumors, even those occurring in different animals, contain the same antigen. Their viral origin can be deduced and sometimes the virus can be identified. Chemically-induced tumors have specific antigens. Embryonic antigens often occur on or in the cancer cells. Some of these may play some role in tumor immunity and others, such as α -fetoprotein, are cytoplasmic. Antigens are usually isolated by dissolving them by procedures similar to those for histocompatibility antigens. Antibodies do not play a role in antitumor immunity: sensitized lymphocytes are the active elements. Certain antibodies protect the tumor against the action of the lymphocytes. In the mouse, such antibodies are usually γ_1 -globulins. Some antitumor-sensitized lymphocytes are cytotoxic, originate in the thymus and can be assayed by the ^{51}Cr test. Others are cytostatic,

generally of type B, may be assayed by the microplaque cytotoxicity method, and may be inhibited by circulating bodies that are probably tumor antigens. Antitumor antibodies have recently been described that can make normal lymphocytes cytotoxic. In the area of human tumors, the presence of antibodies in the blood led to the discovery of Epstein-Barr virus as the agent responsible for infectious mononucleosis and probably for Burkitt's lymphoma. Identical antibodies have been found in the blood of southern Chinese who have a special type of nasopharyngeal cancer. Identical antigens have been found in patients with melanomas and sarcomas of the conjunctiva and bone, but viruses responsible for these tumors have not been identified. Studies using heteroimmune sera have produced evidence of carcinoembryonic antigens (CEA), which exist primarily in cancerous fetal organs, but also in normal persons in trace quantities. Examples are α -fetoprotein, which is found in hepatoma, malignant teratoma, acute hepatitis, and metabolic diseases in children; and carcinoembryonic antigen in intestinal cancers. Other antigens have been described for cancer of the ovaries, nephroblastoma, glioma, and alveolar cancer of the lungs. Some cancer patients have lymphocytes that inhibit tumor growth or that cause lysis of tumor cells for tumors of various organs and melanomas and sarcomas. As with animals, these lymphocytes may be blocked by factors in the blood. Attempts to induce antitumor immunity have consisted mainly of nonspecific therapy; sometimes irradiated tumor cells have been injected. This has proved particularly promising in the treatment of acute leukemias.

- 2416 PSYCHIATRY AND ONCOLOGY: A REVIEW. (E.) Brown, J. H. (Fac. Med., U. Manitoba, Winnipeg, Canada), J. Varsamis, J. Toews and M. Shane. *Can Psychiatr Assoc J* 19(2):219-222, 1974.

There appears to be a definite and complex relationship between malignant disease and emotional disorders of an apparently endogenous kind, not related to gross brain damage, and antedating the discovery of the underlying malignancy. A disproportionately high number of patients treated for various affective disorders, notably depression, develop malignant disease shortly after receiving treatment; the death rate from carcinoma among these patients is significantly higher than predicted by national death rates. There may be an immunological relationship between malignant tissue and nervous tissue. Conversely, psychiatric disorders may be precursors of cancer. Cancer patients have special psychological characteristics which antedate the onset of cancer symptoms, and perhaps of cancer itself; these characteristics have to do with an inhibited life-style, loss of an important relationship, melancholy, and giving up. In addition, serum free fatty acids are raised in both depressive states and in cancer patients during periods of active tumor growth. Insulin, tolbutamide, and reserpine, which lower serum free fatty acids, retard tumor growth. Psychiatric symptoms in patients with an established cancer include tension, depression, anxiety, aggressiveness, and paranoid attitudes. Patients with rapidly progressing cancer tend to evade and repress the anxiety-evoking reality of their ill-

ness more actively than those with relatively good prognoses. The former group also tends to cling less strongly to life, display more depression, anxiety, and tension, be more passive and dependent, and be more aggressive than the latter group. It is suggested that an immunological mechanism may eventually explain the relationship of an underlying malignant disease to a psychiatric illness. (12 references)

- 2418 NEUROBLASTOMA, ITS NATURAL HISTORY AND PROGNOSIS: A STUDY OF 487 CASES. (E.) Wilson, L. M. K. (Res. Dept., Marie Curie Mem. Fdn., England) and G. J. Draper. *Br Med J* 3(5926):301-307, 1974.

The natural history of neuroblastoma and factors affecting survival for this disease were studied in an unselected group of children (268 males, 219 females) reported to cancer registries in Britain between 1962 and 1967. Abdominal swelling was the most common symptom among the youngest children, the incidence of abdominal and thoracic tumors being high in this group. Pain and symptoms related to nerve involvement were more often reported among older children, as were tumors of the spinal cord and brain. The 3-yr survival rate was 23%. There were only five deaths among 110 cases followed for more than 3-yr, confirming the observation that death is unlikely to occur among children who survive more than 2-yr, even when a recurrence occurs. The prognosis and chance of survival after a recurrence were in favor of the girls over the boys. Other factors affecting prognosis included age at diagnosis, site, and histological grade at diagnosis. Histological evidence and analyses of survival and recurrence rates indicate that, in girls, the tumors are more likely to mature into a benign form, thus accounting for the better survival rate among females. (17 references)

- 2417 CARCINOEMBRYONIC ANTIGEN: CHARACTERIZATION AND CLINICAL APPLICATIONS. (E.) Terry, W. D. (Nat'l. Cancer Inst., Bethesda, Md.), P. A. Henkart, J. E. Coligan and C. W. Todd. *Transplant Rev* 20:100-129, 1974.

This review attempts to summarize recent publications concerning the structure of carcinoembryonic antigen (CEA), presents some previously unpublished structural studies, and briefly summarizes work on the clinical applications of CEA assays. An extensive discussion of protein chemistry includes chemical composition, amino acid analysis, and N-terminal amino sequence. A discussion of carbohydrate chemistry includes composition, relationship to heterogeneity, role of carbohydrate in the antigenic site, and relation to carbohydrate in blood group substances. A number of different assays are presently being used to measure the concentration of CEA in plasma or serum or to monitor the purification of CEA. Most are radioimmunoassays. The principal potential uses of CEA are noted, but there is no statistically valid proof at the present time that the CEA test is useful as a diagnostic adjunct when cancer is suspected. (81 references)

- 2419 PARTICIPATION OF LYMPHOCYTES IN VIRAL INFECTIONS. (E.) Wheelock, E. F. (Jefferson Med. Coll., Thomas Jefferson U., Philadelphia, Pa.) and S. T. Toy. *Adv Immunol* 16:124-184, 1973.

The participation of lymphocytes in viral infections is discussed in terms of the problems associated with *in vitro* studies on lymphocytes, morphological alterations in virus-infected lymphocytes, lymphocytopenia in viral infections, virus-lymphocyte associations *in vivo*, the effect of viruses on lymphocytes, immunological defects and their effects on viral infections, the role of lymphocytes in the production of viral disease, and role of lymphocytes in the defense against viral disease. Future studies should be directed toward the elucidation of the precise ways in which lymphocytes act in the host defense. Identification of these mechanisms could lead to the development of therapeutic approaches which could effect rapid recovery from viral infections. (402 references).

- 2420 HORMONES AND NEOPLASIA. (E.) Forrest, A. P. M. (Dept. Surg., U. Edinburgh, Scotland). *J Clin Pathol [Suppl]* 27(7):65-71, 1974.

The author presents a review limited to the hormonal influence on breast cancer. In about 1/3 of cancer cases, generally short-lived remissions are achieved by the administration of androgens or estrogens or the removal of the adrenals or pituitary. Normal development of the human breast requires complex hormonal influences, with estrogen, progesterone, prolactin, growth hormone, and cortisol all playing a part. Hormones can act as promoting agents in neoplastic transformation when given in unphysiologically large doses. Estrogen, progesterone, pituitary hormones, and prolactin all appear to influence the development of spontaneous mammary tumors in female mice and rats. Ovarian hormones also influence the behavior of human breast cancer, and there is evidence for the involvement of the pituitary. In addition, a strong relationship has emerged between the levels of the metabolites of the C-19 (androgenic) steroids in the urine and human breast cancer. The absolute levels of circulating hormones may be less important than the ability of the tumor to synthesize growth-promoting steroids which are locally active. Recent data have indicated a possible role of the sulfating enzymes for estrogens and a high affinity binding protein in the cytoplasm of human breast cancer in the development of breast tumors. (71 references)

- 2421 CAUSAL RELATIONSHIPS BETWEEN ENDOCRINE-METABOLIC VARIABLES IN PATIENTS WITH ENDOMETRIAL CARCINOMA. (E.) Lucas, W. E. (Sch. Med., U. California at San Diego, La Jolla). *Obstet Gynecol Survey* 29(8):507-528, 1974.

The evidence for and against the possibility that endometrial carcinoma may often be the result of a disturbance in endocrine homeostasis is reviewed. The endocrine aspects in the treatment of endometrial carcinoma is discussed. The clinical correlates of endometrial carcinoma are discussed, with emphasis on

obesity, impaired fertility and disturbed menstrual function, impaired glucose tolerance, other endocrine abnormalities, and genetic factors. The relationship between estrogens and endometrial carcinoma is considered in terms of endometrial hyperplasia as a cancer precursor, exogenous and endogenous estrogen (the polycystic ovary syndrome and granulosa-theca cell tumors), cytologic studies, and the ovary and endometrial carcinoma. Progestogens and endometrial carcinoma is also considered, as are animal models, and biochemical and endocrine studies (gonadotropins, growth hormone, estrogen and progesterone metabolism, and enzyme studies). The evidence for a basic derangement of endocrine homeostasis in patients who develop endometrial carcinoma is largely circumstantial. Further documentation and expansion in carefully controlled studies is required, and the establishment of a subhuman primate model for the study of endometrial carcinoma would be helpful. The *in vitro* potentiation of the anti-tumor effects of progestogen by estradiol deserve clinical exploration. (255 references)

- 2422 CARCINOGENESIS BIOASSAY DATA SYSTEM. (E.) Linhart, M. S. (Nat'l. Cancer Inst., Bethesda, Md.), J. Cooper, R. L. Martin, N. Page and J. Peters. *Comput Biomed Res* 7(3):230-248, 1974.

The Carcinogenesis Bioassay Data System (CBDS) provides for the collection, maintenance, and reporting of bioassay information. CBDS was developed for the Carcinogenesis Area of the Division of Cancer Cause and Prevention of the National Cancer Institute. System design and programming were provided by the Data Management Branch of the Division of Computer Research and Technology at NIH. Bioassay investigators provide input data to CBDS. Background data concerning the chemicals and chemical preparations, experimental environments, animal colonies, and animal groups are collected, and observation data are gathered throughout each experiment. A complete pathology report is submitted following the death of each individual animal. These data are essential when evaluating the carcinogenicity of the substances under investigation. Computer programs edit and maintain the data base and prepare reports. CBDS reports are used by NCI in contract administration, and both investigators and NCI use the output to assist in the evaluation of the bioassays.

- 2423 INTRODUCTION: BURKITT'S LYMPHOMA IN AFRICA. (E.) Morrow, R. H. (Harvard Sch. Public Hlth, Boston, Mass.). *Cancer Res* 34(5):1211-1215, 1974.

If the Epstein-Barr virus is a necessary factor in the development of Burkitt's lymphoma, other factors must be involved as well. Evidence implicates malaria as a potential other factor; in particular, taken on a district by district basis within Uganda, the incidence of Burkitt's lymphoma closely parallels that of malaria. A study of 130 Burkitt's lymphoma patients in the East and West Mingo Districts of Uganda showed variations in the incidence rates with time, location, ethnic group, age, and sex. The results indicate that malaria may stimulate the

malignant transformation of Epstein-Barr virus-infected cells. Another study of 56 Ugandan Burkitt's lymphoma patients and controls reinforced the importance of environmental factors in the etiology of the disease. Complement-fixing antibody levels in the sera of 42 Ugandan Burkitt's lymphoma patients and 27 controls indicated that Burkitt's lymphoma patients do not differ from controls in their exposure or response to a wide array of infectious agents. The clinical and immunological aspects of Burkitt's lymphoma are reviewed with regard to criteria for diagnosis, clinical features of the disease, immunological features, and new information relating to the natural history of the disease. (No references)

- 2424 BREAST CANCER IN JAPANESE MIGRANTS. (E.)
Anonymous. *Br Med J* 2(5924):134-135, 1974.

The persistently low mortality rate from breast cancer among Japanese Americans in 1949-52 and again 10 years later was taken as evidence of the importance of constitutional factors in the etiology of the disease. However, data obtained in the national cancer survey indicated that by 1969-71, the incidence of breast cancer among Japanese American women in the San Francisco Bay area had risen to half that in white American women and was about five times as high as in native Japanese. The increased rate was due almost entirely to an increase among American-born, as opposed to immigrant, Japanese. Thus, environmental factors which are capable of modification apparently have played a large part in maintaining the low incidence of breast cancer in oriental women. The protective effects of pregnancy before age 30 and of early first parity, both of which favor Japanese-born migrants, may explain some of the difference in breast cancer rates. A dietary hypothesis might also be invoked to explain the differential synthesis of the anticarcinogen estriol versus the carcinogens estrone and estradiol (there is relatively more estriol in comparison with the amount of estrone and estradiol in the urine of young oriental women than in the urine of white American women). The adoption of more Western patterns of fertility and diet by present and future generations of American-born Japanese may contribute leads into the etiological role of heredity and environmental factors in breast cancer. (11 references)

- 2425 HEREDITARY FACTORS IN LEUKEMIAS. (Fr.)
Gisselbrecht, S. (St. Louis Hosp., Paris
France). *Rev Prat* 23(1):19-25, 1973.

Genetic transmission of leukemia is demonstrated by the occurrence of two or more cases in the same family and the relative rarity of the disease. Of 102 instances of familial leukemia reviewed, 77 were leukemias of the same type and 41 were acute leukemia. The frequency of familial leukemia is considerably greater for twins, and the chances of the second twin having leukemia is greater if the first twin develops the disease at a very early age. The risk is also much greater for monozygotic than for dizygotic twins: of 21 pairs of afflicted twins, only three were known to be dizygotic. Acute leukemia is often associated with certain genetic

diseases, notably mongolism. There seems to be a higher frequency of trisomy G in leukemic families, and an association between acute leukemia and trisomy D, Klinefelter's syndrome, and other karyotypic anomalies has been demonstrated. Familial involvement has been observed for other malignant hemopathies, such as Hodgkin's disease, myelomas, Waldenstrom's disease, and asymptomatic monoclonal immunoglobulinemia. An anomaly of chromosome 12 seems consistently associated with chronic myeloid leukemia, but the anomaly is acquired rather than inherited. Genetic factors probably play only a limited role in the development of leukemia. An *in vitro* study of leukemogenic viruses in chickens and mice provides evidence of cell genes able to protect the cell from infection by leukemogenic viruses. There is some evidence that leukemias and sarcomas may be genetically transmitted in a species, probably by germ cells. The expression of such endogenous viruses may be controlled by factors in the cell, as has been reported for birds and mice. Induced leukemia in the mouse was used to show that a complex genetic system involving at least 3 genes, controls the development of leukemia. However, experimental systems that confirm the existence of genetic control of leukemogenesis are difficult to extrapolate to human leukemia. (11 references)

- 2426 PHYSIOLOGICAL RESPONSES TO INHALATION OF
CIGARETTE SMOKE AND OTHER IRRITANT GASES
AND AEROSOLS. (E.) Widdicombe, J. G. (St. George's
Hosp. Med. Sch., London, England). *Boll Soc Ital
Biol Sper* 49(18):1973.

When irritant gases and aerosols penetrate into the respiratory tract and lungs a complex system of reflexes is activated by stimulation of receptors in and under the epithelial cell layer. Many different groups of receptors may be excited, including those in the nose, epipharynx, larynx, trachea and larger bronchi, and interpulmonary bronchi. The net reflex responses will depend on the interaction and integration of discharges in the various afferent pathways, but breathing, bronchomotor tone, laryngeal calibre, mucus secretion, the cardiovascular system and sensation may all be involved. Although there have been many studies on the sites and amounts of deposition of various inhaled gases and aerosols, these investigations have not usually been related to the physiological changes caused by the deposition; in any case such studies cannot easily be performed in man and have, necessarily, been confined to experimental animals. (29 references)

- 2427 THE CAUSATIVE ROLE OF HERPESVIRUS TYPE 2
IN CERVICAL CANCER. (E.) Melnick, J. L.
(Baylor Coll. Med., Houston, Tex.), E. Adam and W. E.
Rawls. *Cancer* 34(4):1375-1385, 1974.

Antibodies against herpesvirus type 2 are more frequently found in women with cervical cancer than in matched control women. This appears to be true not only for invasive carcinoma of the cervix but also for carcinoma *in situ* and cervical dysplasia. Since both cervical cancer and herpes type 2 infections are related to attributes associated with venereally

transmitted agents, the association between the virus and the cancer could represent one of covariability. However, recent studies, including the comparison of cervical cancer patients with matched breast cancer patients of the same social group, support the hypothesis of a causal relation of the virus to cervical cancer. Also supporting the hypothesis are the recent findings of antibodies to herpesvirus-induced nonvirion antigens in cervical cancer patients. An important next step in furthering knowledge of the role of herpesvirus in human cancer would be carefully executed prospective studies: to determine the relative risk of developing the disease among women with and without a past herpesvirus type 2 infection; and to determine the occurrence of antibodies to herpesvirus nonvirion antigens in relation to cervical neoplasia and to evaluate the diagnostic and/or prognostic value of antibody patterns to the virion and nonvirion antigens. From these data it should be possible to characterize high-risk women who can be followed more carefully and to whom existing preventive measures could be more intensively applied. (52 references)

- 2428 PATHOGENESIS OF LIVER CANCER. (E.) Farber, E. (Temple U. Sch. Med., Philadelphia, Pa.). *Arch Pathol* 98(3):145-148, 1974.

The highlights of some newer developments in the study of the pathogenesis of liver cancer in experimental animals are presented. Emphasis has been given to the probable occurrence of both somatic mutation and altered differentiation, cellular evolution from initiated preneoplastic cells to malignant neoplasia, interruption of differentiation in early new hepatocyte populations, and the appearance of a new antigen marker, found so far only in hepatocytes considered to be preneoplastic and premalignant and in primary liver cancer induced by one of several carcinogens. The possible value of this model for the development of liver cancer in man and for carcinogenic processes in other organs is delineated. (27 references)

- 2429 IS HODGKIN'S DISEASE INFECTIOUS? (E.) Vianna, N. J. (New York St. Dept. Hlth., Albany). *Cancer Res* 34(5):1149-1155, 1974.

Evidence from a variety of different epidemiological studies suggests that Hodgkin's disease is an environmental disease. Recently, four groupings of Hodgkin's disease have been described in which cases were linked to other cases, either directly or through a single healthy intermediary. The characteristics of these groupings and those of the epidemic curve in Albany County, N.Y., suggest that Hodgkin's disease may be infectious under certain circumstances. This possibility is further supported by the observation that prior tonsillectomy might be a predisposing factor to the development of this disease. Although the features of Hodgkin's disease are consistent with an infectious etiology, the author stresses the need for new methodological approaches in objective epidemiological studies for further evaluation of this hypothesis. (66 references)

- 2430 EVALUATION OF SHORT-TERM TESTS FOR CARCINOGENICITY. (E.) Stoltz, D. R. (Food Res. Labs., Health Protection Branch, Ottawa, Canada), L. A. Poirier, C. C. Irving, H. F. Stich, J. H. Weisburger and H. C. Grice. *Toxicol Appl Pharmacol* 29:157-180, 1974.

The authors present a review which evaluates 8 endpoints that have been proposed as parameters in short-term tests to detect chemical carcinogens. Tests proposed for detecting carcinogenic activity rapidly yet reliably include prescreening chemicals for: 1) accelerated tumor formation, 2) chromosome aberrations, 3) mutagenesis, 4) DNA repair synthesis, 5) teratogenesis, 6) *in vitro* cell transformation, 7) reaction with nucleic acids and 8) cytological alterations. Each of these test systems is critically evaluated with respect to its possible relevance to the carcinogenic process and to its practicality. Three of the tests, mutagenesis, DNA repair synthesis, and *in vitro* cell transformation were found to offer considerable promise as prescreens for chemical carcinogens. Of the three promising tests, cell transformation is probably the most directly related to the carcinogenic process. However, compared to mutagenesis and DNA repair, the cell transforming activities of relatively few carcinogens have been reported. (204 references)

- 2431 CURRENT CONCEPTS IN CHRONIC MYELOGENOUS LEUKEMIA. (E.) Stryckmans, P. A. (Tumor Ctr., Free U., Brussels, Belgium). *Semin Hematol* 11(2):101-128, 1974.

The basic and emerging concepts pertaining to chronic myelogenous leukemia (CML) are discussed, along with the classical and more recent therapeutic procedures. Specific topics include: the persistence of regulatory mechanisms for myelopoiesis in CML, the transit time in the blood of polymorphonuclear cells (PMN) in CML, the functional capacity of PMN, the Philadelphia (Ph¹) chromosome, the clonal origin of CML, the proliferation of myeloid cells in CML, and the blastic transformation or blast-cell crisis. A large number of drugs have some activity in CML, including busulfan (myleran), dibromomannitol (DMB), and hydroxyurea. Other modes of treatment have included splenic irradiation, extracorporeal irradiation of the blood (ECIB), leukapheresis, and splenectomy. Prophylactic treatment of the blastic transformation in CML is also discussed, as is irradiation of the leukemic cells. None of the classical treatments have so far significantly increased the survival of CML patients. The possible therapeutic effect of immunotherapy deserves further evaluation, and intensive chemotherapy offers some hope for the future. (159 references)

- 2432 HUMAN RADIOBIOLOGY. (E.) Bond, V. P. (No affiliation). *Curr Top Radiat Res* 9:40-46, 1974.

A large amount of data is available on the early response of man to different doses of radiation, although information is incomplete regarding the effect

of dose rate, the behavioral responses, the response to high LET radiations, and the radiosensitivity of bone marrow and bowel stem cells. A great deal of information is available on internal emitters, and an enormous amount of work is being done on the effects of radiation on experimental tumors and the surrounding normal tissues. Lack of knowledge regarding the growth characteristics of human tumors will impede the application of the experimental data to human beings. More work is needed on the combined use of chemotherapy and radiotherapy and on the immune response as a factor in radiotherapy. Particulate radiations such as fast neutron beams, proton beams, and pion beams will be studied in the next decade. The effects of improved depth-dose patterns will be determined by the location of the dose-limited normal tissue. There are virtually no data on the genetic effects of radiation in the human being. The most important of the late effects are malignancies. Acute and chronic myelocytic leukemia, and cancers of the thyroid, breast, lung, and bronchus are well-documented sequelae of exposure at high doses and dose rates. With the exception of fetal irradiation, there are no data on the risk of cancer in humans following exposure at doses and dose rates commensurate with the standards. Extrapolations from data on the incidence of leukemia among Japanese exposed to the atomic bomb is complicated by the fact that the radiations from the weapons in Hiroshima and Nagasaki were different. If information obtained from animal experimentation cannot be realistically applied to human beings, the reasons for obtaining such data must be questioned. (10 references)

2433 THE CANCEROUS ACTION OF ARSENIC AND NICKEL. (Ger.) Konetzke, G. W. (Cent. Inst. Occupational Med., Berlin, Germany). *Arch Geschwulstforsch* 44(1):16-22, 1974. (54 references)

2434 THE VAGARIES OF ERYTHROLEUKAEMIA. (E.) Karle, H. (U. Hosp. Copenhagen, Denmark), S. A. Killmann, M. K. Jensen and J. B. Nielsen. *Acta Med Scand* 196(4):245-253, 1974. (24 references)

2435 OVARIAN TUMORS IN YOUNG WOMEN. (Pol.) Michalkiewicz, W. (Inst. Gynecol., Psonan, Poland), M. Wolna and T. Pisarski. *Patol Pol* 25(1):291-299, 1974. (15 references)

2436 THE RELATIONSHIP BETWEEN CHRONIC GASTRITIS, GASTRIC ULCERATION AND CARCINOMA OF THE STOMACH. A HISTORICAL REVIEW. (E.) Bock, O. A. A. (Tygerberg Hosp., Tiervlei, South Africa). *S Afr Med J* 48(49):2063-2066, 1974. (37 references)

2437 FELINE LEUKEMIA VIRUS AND PUBLIC HEALTH AWARENESS. (E.) Hardy, Jr., W. D. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.), A. J. McClelland, P. W. Hess and E. G. MacEwen. *J Am Vet Med Assoc* 165(11):1020-1021, 1974. (22 references)

2438 PROBLEMS OF LOW DOSES OF CARCINOGENS. (E.) Rall, D. P. (Natl. Inst. Environ. Hlth. Sci., Research Triangle Park, N.C.). *J Wash Acad Sci* 64(2):63-90, 1974. (No references)

2439 RADIUM IN MAN. (E.) Evans, R. D. (Massachusetts Inst. Technol., Cambridge). *Health Phys* 27(5):497-510, 1974. (35 references)

2440 PRESENT ASPECTS OF THE IMMUNOLOGY OF CANCER. (E.) Romieu, C. (St. Eloi Hosp., Montpellier, France) and B. Serrou. *Int Surg* 59(8):393-396, 1974. (6 references)

2441 RAUWOLFIA DERIVATIVES AND BREAST CANCER. (E.) Anonymous. *Lancet* 2(7892):1315-1316, 1974. (6 references)

2442 COLPOSCOPIC EVALUATION OF STIBESTROL EXPOSED YOUNG WOMEN. (E.) Marlow, J. L. (George Washington U. Sch. Med., Washington, D. C.). *Med Ann DC* 43(10):503-506, 1974. (11 references)

2443 REFLECTIONS IN TOXICOLOGY. (E.) Cranmer, M. F. (Natl. Ctr. Toxicol. Res., Jefferson, Ark.). *J Wash Acad Sci* 64(2):158-179, 1974. (30 references)

- 2444 THE EFFECT OF DIETARY PROTEIN DEFICIENCY ON THE ABILITY OF ISOLATED HEPATIC MICROSOMES TO ALTER THE MUTAGENICITY OF A PRIMARY AND A SECONDARY CARCINOGEN. (E.) Czygan, P. (Mt. Sinai Sch. Med., City U. New York, N.Y.), H. Greim, A. Garro, F. Schaffner and H. Popper. *Cancer Res* 34(1):119-123, 1974.

The capacity of isolated hepatic microsomes from Swiss-Webster mice to alter mutagenicity for bacteria of the primary carcinogen, *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, and the secondary one, dimethylnitrosamine, was studied. Microsomal inactivation of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and activation of dimethylnitrosamine were decreased by protein- and protein-choline-deficient diets, and this decrease paralleled the reduction in microsomal cytochrome P450 content produced by these diets. The results obtained with this *in vitro* assay indicate that the status of the microsomal biotransformation system which can be influenced by nutritional factors determines the mutagenicity of the primary and secondary carcinogens tested.

- 2445 INDUCTION OF MALIGNANT KIDNEY TUMORS IN RATS WITH STREPTOZOTOCIN. (E.) Mauer, S. M. (U. Minnesota Med. Sch., Minneapolis), C. S. Lee, J. S. Najarian and D. M. Brown. *Cancer Res* 34(1):158-160, 1974.

Diabetes was induced in rats with streptozotocin (65 mg/kg i.v.) and alloxan (40 mg/kg i.v.) and the tumorigenic effects of these two compounds were compared. Of 130 Lewis and Sprague-Dawley rats who survived the induction of diabetes with streptozotocin, 56 were sacrificed within eight months of streptozotocin administration and three were found to have renal tumors. Twenty-four of 74 (30.8%) rats sacrificed more than eight months after the induction of diabetes with streptozotocin had grossly visible renal tumors. The lesions were epithelial in type and, although rarely invasive, had malignant cytological characteristics. Two of these animals had gross tumor spread to the liver and lungs. Forty percent of the renal tumors were bilateral. No tumors were found in 72 rats surviving diabetic induction with alloxan and 260 littermate controls. It is concluded that streptozotocin can induce renal cancer in rats.

- 2446 ACUTE LEUKAEMIA IN TWO GENERATIONS FOLLOWING CHRONIC EXPOSURE TO BENZENE. (E.) Aksoy, M. (Istanbul Med. Sch., Turkey), S. Erdem, G. Erdogan and G. Dincol. *Human Hered* 24(1):70-74, 1974.

Two cases of acute leukemia, one lymphoblastic and the other myeloblastic, following chronic exposure (4 and 6 yr, resp.) to benzene in two relatives, a man and his paternal uncle, are presented. The possibly significant role of genetic predisposition is discussed. Although both patients had some chromosomal abnormalities, these could not be incriminated as the cause of the leukemia. It is concluded that some genetic factors were triggered by chronic exposure to benzene in these patients.

- 2447 RADIOLOGICAL STUDY OF CANINE STOMACH CANCER INDUCED BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Noguchi, M. (Tokyo Med. Dental U., Japan), T. Yamada, H. Ichikawa, N. Tanaka, T. Kawachi and K. Kogure. *Gann* 65(2):93-102, 1974.

An aqueous solution of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine was given p.o. for 15 months to four 3-month-old mongrel dogs, 167 µg/ml for the first month and 83 µg/ml for the following 14 months, in place of drinking water. Follow-up examination of their stomachs was made successively by radiography, endoscopy, and biopsy. Double-contrast photography revealed fine gastric mucosal damage. Dogs were sacrificed when they became moribund during the follow-up period. Eight cancers and one leiomyosarcoma were found histologically in the cardiac and pyloric portions of the stomach. Seven of these nine lesions were visualized clearly in radiographs. Diagnosis of the lesions was six cancers or suspected cancers, and one polyp. The malignant lesions, diagnosed radiologically, were classified into three types: flat, ulcerative, and polypoid. It was found that deeply ulcerative lesions were advanced gastric cancer while flat or slightly ulcerative lesions were early cancer.

- 2448 IS SHORT-FIBERED ASBESTOS DUST A BIOLOGICAL HAZARD? (E.) Gross, P. (Med. U. South Carolina, Charleston). *Arch Environ Health* 29(2):115-117, 1974.

It has been the finding of research laboratories in Germany, England, South Africa, and the U.S that short-fibered asbestos dust, that is, less than 5µ in length, is incapable of causing fibrosis or cancer. This finding, in conjunction with the failure of different laboratories in the United Kingdom and in this country to discern abnormalities following prolonged asbestos feeding to rats, should lead to the abandonment of the present concept that malignant mesotheliomas and gastrointestinal cancers arise from the ingestion of asbestos dust cleared from the lungs. These negative results should also allay the fears that have been raised as a result of the finding of ultramicroscopic mineral fibers in certain beverages and drinking water.

- 2449 7,12-DIMETHYLBENZ(a)ANTHRACENE RETENTION IN THE RAT SUBMANDIBULAR GLAND FOLLOWING INTRAGLANDULAR INJECTION. (E.) Schmutz, J. A. (Sch. Med., State U. New York, Buffalo), A. C. Brownie and A. P. Chaudhry. *Cancer Res* 34(3):576-580, 1974.

The relative concentration of radioactive carbon retained in the male Sprague-Dawley rat submandibular gland and its cell fractions following the intraglandular injection of 12-¹⁴C-7,12-dimethylbenz(a)-anthracene (0.1 mg) was determined at periods ranging from 6 hr to 6 weeks by liquid scintillation spectroscopy. Ethyl acetate extracts of gland homogenates and cell fraction suspensions were similarly analyzed to determine the degree of binding of the

carcinogen in this tissue. Less than 30% of the total hydrocarbon injected was found in the glands of animals sacrificed during the 1st week. The carcinogen content of the gland declined to 13, 7, and 5%, resp., at 2, 4, and 6 weeks after treatment. A minimum of 65% of the radioactivity in this tissue was extractable from the homogenates of all the groups examined. The nuclear fraction contained higher values of ^{14}C than other fractions during the 1st day, whereas, at subsequent time periods, more isotope was found in the cytosol fraction.

2450 DIFFERENTIAL RESPONSE OF SNELL'S AND C57 BLACK MICE TO CHRONIC INHALATION OF CIGARETTE SMOKE. PULMONARY CARCINOGENESIS AND VASCULAR ALTERATIONS IN LUNG AND HEART. (E.) Leuchtenberger, C. (Swiss Inst. Exp. Cancer Res., Lausanne) and R. Leuchtenberger. *Oncology* 29(2):122-138, 1974.

The influence of genetic differences between mouse strains, such as presence or absence of spontaneous lung cancers or of spontaneous vascular lesions in lung and heart, on the response to chronic inhalation of cigarette smoke was investigated. After inhaling whole cigarette smoke or its gas vapor phase, Snell's mice disclosed a higher frequency and earlier occurrence of lung adenocarcinomas than controls, while C57 Black mice did not develop lung adenocarcinomas. On the other hand, after inhalation of whole cigarette smoke, C57 Black mice disclosed a higher frequency of vascular changes in lung and heart, while there was no such effect in Snell's mice. Since Snell's controls developed spontaneous lung adenocarcinomas but no vascular alterations, while C57 Black controls had no spontaneous lung cancers but vascular changes, the results indicate an enhancing effect of cigarette smoke on existing abnormalities in these two strains.

2451 EFFECT OF ACROLEIN ON THE DEVELOPMENT OF CHROMOSOME LESIONS INDUCED BY 5-FLUORODEOXYURIDINE AND MALEIC HYDRAZIDE IN *VICIA FABA*. (Fr.) Valadaud-Barrieu, D. (Res. Dept., SEITA, Paris, France) and C. Izard. *C R Acad Sci [D] (Paris)* 278(12):1569-1572, 1974.

To define the transitory depressive effects of acrolein on cell division, its effects in association with 5-fluorodeoxyuridine and with maleic hydrazide were studied. Experiments were carried out on meristems of lateral roots of *Vicia faba* var. Aguadulce. For analysis of hydrazine-induced anomalies, roots were pretreated with colchicine (0.05%) 2 hr 30 min before fixation with acetic acid-alcohol (3:1). Feulgen stain was used throughout interactions of 0.62 or 0.7 μM 5-fluorodeoxyuridine and 0.02 mM acrolein were tested in pretreatment, post-treatment, or in mixture for 1 hr. Maleic hydrazide was used at 0.22 and 0.26 mM for 2 hr, either pre- or post-treatment. Interactions between 5-fluorodeoxyuridine and maleic hydrazide were studied by replacing acrolein with 0.5 mM maleic hydrazide. The experiments show that acrolein is capable of inhibiting the action of 5-fluorodeoxyuridine and maleic hydrazide; the latter seems to act like acrolein with respect

to 5-fluorodeoxyuridine. The possibility of interaction between these three substances exists. While acrolein and hydrazide increase the duration of DNA synthesis, it does not appear that this property can account for the apparent decrease in the activity of 5-fluorodeoxyuridine, since the latter induces lesions during the G_2 phase of the cycle and after synthesis of DNA. The inhibitory effect of acrolein on maleic hydrazide is at least partially explained by a competition between the two products for the sites of thiol function. It is possible, however, that acrolein exerts a stabilizing effect on the DNA structures at the level of the lesions induced by 5-fluorodeoxyuridine and maleic hydrazide.

2452 INDUCTION OF ADENOFIBROSIS AND HEPATOMAS OF THE LIVER IN BALB/cJ MICE BY POLYCHLORINATED BIPHENYLS (AROCLOL 1254). (E.) Kimbrough, R. D. (Ctr. Dis. Control, Atlanta, Ga.) and R. E. Linder. *J Natl Cancer Inst* 53(2):547-552, 1974.

Two groups of 50 BALB/cJ inbred male mice were fed 300 ppm of a polychlorinated biphenyl, Aroclor 1254, in the diet for 11 and 6 months, resp. The 6 months of feeding were followed by 5 months of recovery. Two additional groups of 50 mice each were fed plain chow. All 22 surviving mice fed Aroclor 1254 for 11 months had greatly enlarged liver representing 25% of their body weight, whereas those fed the experimental diet for 6 months only had slightly, but significantly, enlarged livers. Adenofibrosis was observed in livers of all 22 mice fed Aroclor 1254 for 11 months but not in the other groups. Of these 22 mice, nine had 10 hepatomas measuring 0.1-1.5 cm in diameter. One of 24 surviving mice fed Aroclor 1254 for only 6 months had a hepatoma 0.3 cm in diameter. No controls had hepatomas.

2453 REACTIONS BETWEEN ACTIVATED BENZO(a)PYRENE AND NUCLEOPHILIC COMPOUNDS, WITH POSSIBLE IMPLICATIONS ON THE MECHANISM OF TUMOR INITIATION. (E.) Cavalieri, E. (U. Nebraska Med. Ctr., Omaha) and R. Auerbach. *J Natl Cancer Inst* 53(2):393-397, 1974.

Benzo(a)pyrene activated by one-electron oxidation with iodine or ferric ion (an essential component of cytochrome P-450), or by a presumed electrophilic oxygen obtained from ferric chloride and hydrogen peroxide, produced cationic species which on subsequent trapping with suitable nucleophiles gave only 6-substituted benzopyrenes. The radical cation of benzo(a)pyrene could be generated *in vivo* by transition metal-containing hydroxylase enzymes before metabolic oxidation. The resulting intermediate with significant positive-charge localization at the 6-position could be trapped by proximate cellular nucleophiles. A possible alternate mode of activation *in vivo* is the attack of an electrophilic oxygen species at one of the substituting positions (1, 3, or 12) complementary to the 6-position. The resulting cation would possess sufficient charge localization at the 6-position to promote binding with cellular nucleophiles.

2454 EFFECT OF A CARCINOGENIC ORAL DOSE OF 7, 12-DIMETHYLBENZ(A)ANTHRACENE ON RECEPTOR BINDING OF ESTRADIOL-17 β IN UTERUS AND MAMMARY TISSUE THROUGHOUT LACTATION IN THE RAT. (E.) Keightley, D. D. (Dept. Biol., Univ. Windsor, Ontario, Canada) and A. B. Okey. *Cancer Res* 34(3):609-12, 1974.

Ingestion of a single 15 mg dose of 7,12-dimethylbenz(a)anthracene (DMBA) by lactating Sprague-Dawley rats increased the number of estrogen receptor sites in mammary cytosol fraction and decreased slightly the intrinsic association constant for the estradiol-receptor interaction. These effects were first seen 2 days after treatment, but there were no differences between control and DMBA-treated animals at 20 days after treatment. In the uterus there were no significant differences in the number of binding sites between control and DMBA-treated animals at any point during lactation. Direct measurements of estradiol-17 β by a radioreceptor assay indicated reduced levels of the endogenous steroid in both mammary gland and uterus following DMBA treatment, but such a reduction could not account for the apparent increase in binding sites in mammary tissue. More likely, there was an increase in the proportion of epithelial cells to fat cells in the mammary glands of DMBA-treated rats, increasing the total amount of estrogen receptor in the gland.

2455 EFFECT OF CHLORAMPHENICOL AND DEXTRAMYCINE ON THE TOXICITY OF CARCINOGENIC HYDROCARBONS. (E.) Shabad, L. M. (Inst. Exp. Clin. Oncol., USSR Acad. Med. Sci., Moscow), G. A. Belitsky and T. A. Bogush. *Z Krebsforsch* 82(1):13-23, 1974.

Chloramphenicol and its isomer dextramycin considerably decreased the toxic effect of 0.1 μ g/ml 7,12-dimethylbenz(a)anthracene (DMBA) and 1.0 μ g/ml benz(a)pyrene on mouse embryo fibroblast-like cells grown *in vitro*. Chloramphenicol seems to be more effective at the toxic concentration of 500 μ g/ml than at the nontoxic concentration of 100 μ g/ml. The toxic effect of chloramphenicol (500 μ g/ml) did not cumulate to that of DMBA. The number of cells in cultures treated with both agents was always higher than that in cultures incubated with the carcinogen alone. The same protective effect was exhibited by dextramycin. The destruction of the adrenal cortex in rats receiving large doses of DMBA was also prevented by pretreatment with either of the protective compounds.

2456 ULTRAVIOLET HYPOCHROMISM IN THE INTERACTION SYSTEMS OF DNA AND CARCINOGENIC 2-ANTHRAMINE AND ITS RELATED COMPOUNDS. (E.) Okano, T. (Pharmaceutical Inst., Tohoku U., Sendai, Japan), S. Takenaka, T. Horie and T. Kano. *Gann* 65(1):33-44, 1974.

The mode of electronic interaction between calf-thymus DNA and 2-anthramine, 1-anthramine, 9-anthramine, and N,N-dimethyl-2-anthramine was studied. With mixtures containing low concentrations of DNA and 2-anthramine, the absorption intensity of the mixture in the region around 260 nm decreased with time. This hypochromic change was smaller in systems con-

taining DNA and 1- or 9-anthramine or N,N-dimethyl-2-anthramine; unlike 2-anthramine, the latter three anthramines do not induce skin tumors when applied to the skins of animals. The orderly secondary nature of the DNA was indispensable in the production of hypochromism, and there was an optimum salt concentration (3.5 mM NaCl and 0.25 mM trisodium citrate) for the spectroscopic change. The degree of hypochromism expressed by the integrated intensity paralleled the degree of spectral overlapping of the interactants. The specificity of 2-anthramine with respect to its carcinogenic activity can be explained in terms of the specificity of its electronic structure.

2457 PANCREATIC REGENERATION CAUSED BY ETHIONINE IN THE GUINEA PIG. (E.) Wenk, M. L. (Microbiological Assoc., Bethesda, Md.), J. K. Reddy and C. C. Harris. *J Natl Cancer Inst* 52(2):533-538, 1974.

Hartley strain guinea pigs were given 10 daily i.p. injections of either ethionine (0.01, 0.04, or 0.07 g/kg) or methionine (0.08, 0.25, or 0.5 g/kg) while on a protein-free diet. From day 11, they were fed a protein-sufficient diet. The highest doses of either ethionine or methionine caused 80% mortality. At better tolerated doses, focal pancreatic necrosis followed by regeneration was induced by ethionine but not by methionine. Ethionine caused nucleolar fragmentation, an increase in free ribosomes, and focal cytoplasmic degradation, all of which were reversed by 30 days. Regeneration of pancreatic acinar cells and pancreatic duct cells was assessed at 10, 12, 16, and 30 days from the start of the experiment by counting either metaphases arrested by colchicine or nuclei labeled by 3 H-thymidine in autoradiograms. Ethionine caused maximal regeneration of acinar cells at 16 days. No significant regeneration of duct cells was detected on those days monitored.

2458 MUTAGENESIS BY N-METHYL-N-NITROSO-N'-NITROGUANIDINE IN SYNCHRONIZED CULTURES OF *MYCOBACTERIUM PHLEI*. (E.) Konickova-Radochova, M. (Inst. Microbiol., Czechoslovak Acad. Sci., Prague) and J. Konicek. *Folia Microbiol (Praha)* 19(1):16-23, 1974.

Conditions for the maximum induction of back mutations by N-methyl-N-nitroso-N'-nitroguanidine (nitrosoguanidine) were studied in auxotrophic mutants of *Mycobacterium phlei*. In asynchronous cultures, the effects of pH, buffer molarity, and concentration of and exposure time to nitrosoguanidine were studied. Between 6 and 10, pH did not affect the induction of back mutations, but with increasing pH up to 9, the lethal effect of nitrosoguanidine on cells was increased. Protracted treatment with nitrosoguanidine did not affect the induction of back mutations; nor did the buffer molarity. The most efficient induction of back mutations in several strains of *M. phlei* was achieved after treatment with 0.5 or 1 mg nitrosoguanidine/ml for 20 min at pH 6. Based on these results, a procedure was developed for inducing back

mutations in synchronous cultures. The results were evaluated by determining the frequency of back mutations as a function of time during synchronous culture growth. With one strain of *M. Phlei*, the maximum number of mutations occurred after 30 min, while with another strain the maximum number occurred after 105 min; the results were identical with both single and double auxotrophic mutants.

- 2459 REACTION OF DRUGS WITH NITROUS ACID AS A SOURCE OF CARCINOGENIC NITROSAMINES. (E.) Lijinsky, W. (Biol. Division, Oak Ridge Natl. Lab., Tenn.). *Cancer Res* 34(1):255-258, 1974.

Twelve common drugs that are tertiary amines reacted with nitrite in aqueous solution at pH 3 to 4 to form dialkyl nitrosamines that are known carcinogens. The drugs examined were aminopyrine (analgesic), chlorpheniramine and methapyrilene (antihistaminics), chlorpromazine and dextropropoxyphene (tranquilizers), tolazamide (hypoglycemic), quinacrine (antimalarial), lucanthone (antischistosomaliasis), cyclizine (for motion sickness), disulfiram (antialcoholic), and methadone (narcotic). Aminopyrine gave dimethylnitrosamine in 30% yield or higher at all concentrations down to 50 ppm (with 25 ppm nitrite). The other product of this reaction was the nitrite salt of 4-hydroxyantipyrine. The other drugs, when present at 0.01 M with 0.04 M nitrite, formed nitrosamines in yields ranging from 0.03% for dextropropoxyphene to 2.4% for lucanthone in 4 hr at 37 C.

- 2460 CARCINOGENIC ACTIVITY OF SERPENTINE ASBESTOS AFTER INTRAPLEURAL ADMINISTRATION IN RATS. (Rus.) L. N. Pylev (Inst. Exp. Clin. Oncol. Moscow, USSR). *Vopr Onkol* 20(4):47-53, 1974.

The tumorigenic activity of Soviet chrysotile from one location was studied. Chrysotile dust removed from electrofilters at an asbestos-concentration plant was introduced into the right pleural cavity of ether-anesthetized rats. Each animal received 3 doses of 20 mg asbestos dust in 0.5 ml of physiological saline at one month intervals. Lungs, sections of the parietal pleura, and other organs were fixed in 10% neutral formalin solution and imbedded in paraffin. Serial sections were stained with hematoxylin-eosin, picrofuchsin, and Prussian blue in iron. Chronic interstitial pneumonia, focal abscessing pneumonia, purulent bronchitis with peribronchial and perivascular lymphoid deposits, and focal adenomatous proliferation of the bronchial epithelium were observed. These changes were analogous to those observed in experiments with polycyclic hydrocarbons. Asbestos granulomas on the surface of the lungs were observed in the majority of rats. From 2-2.5 months after 3 intrapleural doses of dust, morphological changes were observed in 7 rats. From 8-24.5 months after the inoculation, diffuse hyperplasia and proliferation were observed in 45, focal adenomatous proliferation in 10, sarcoma-like mesothelioma in 13, adenomatous-papillary mesothelioma in 6, and mixed mesothelioma in 12. The first mesothelioma was observed in a rat who died 8 months after the experiment began. Of 46 rats who

died after 8-17 months, mesotheliomas were observed in 13 (28.26%), while of 21 who died after 18-24.5 months, mesotheliomas occurred in 15 (71.43%). Considerable structural polymorphism was observed in the mesotheliomas. The asbestos dust is very similar to dust of polluted air in industrial plants.

- 2461 PROTECTION BY A SMALL DOSE OF CARBON TETRACHLORIDE AGAINST THE TOXIC EFFECTS OF DIMETHYLNITROSAMINE IN RATS. (E.) Pound, A. W. (Dept. Path., U. Queensland, Brisbane, Australia) and T. A. Lawson. *Br J Exp Pathol* 55(2):203-212, 1974.

A single intragastric dose of carbon tetrachloride (CCl₄) (0.01-2.5 ml/kg) protected male Sprague-Dawley rats against the toxic effects of dimethylnitrosamine (DMN) injected i.p. This appeared to be due to a reduction in the levels of DMN-demethylase, a microsomal enzyme involved in the metabolism of DMN. An increase in the LD₅₀ of DMN and a reduction in the demethylase levels were observed within 20 min of CCl₄ administration. The changes were maximal within 12 hr and persisted until 48 hr postadministration. The enzyme activity began to increase after about 60 hr and returned to normal 120 hr after CCl₄ administration; the LD₅₀ of DMN returned to normal within the same time period. The LD₅₀ of DMN increased rapidly as the dose of CCl₄ increased from 0.01-0.16 ml/kg, after which the increase with dose leveled off. The converse was found with DMN-demethylase, which fell rapidly as the dose of CCl₄ increased; it also leveled off with doses of CCl₄ higher than 0.16 ml/kg. CCl₄ also prevented the development of the hepatocellular necrosis which normally follows the administration of toxic doses of DMN.

- 2462 EFFECT OF DIETARY FAT, ANTIESTROGEN, AND ANTIPROLACTIN ON THE DEVELOPMENT OF MAMMARY TUMORS IN RATS. (E.) Chan, P. C. (American Hlth. Fdn., New York, N.Y.) and L. A. Cohen. *J Natl Cancer Inst* 52(1):25-30, 1974.

After a single oral dose of 5 or 10 mg 7,12-dimethylbenz[*a*]anthracene (DMBA), female Sprague-Dawley rats fed a high fat (HF) semisynthetic diet developed mammary tumors earlier and in greater numbers than rats fed a low fat (LF) diet. The average growth rate, based on body wt, was comparable in both groups. To determine whether the dietary effect might be mediated by changes in hormones such as estrogen and prolactin, DMBA-pretreated rats fed HF and LF diets were given the antiprolactin drug CB-154 (3 mg/kg s.c.) or the antiestrogen drug U11,100A (1 mg/kg s.c.) and breast tumor incidence was measured. Whereas breast tumor development was decreased in extent and speed by the antiestrogen, the differential incidence of tumors in rats fed an HF diet remained higher in comparison to rats on a LF diet. In contrast, the antiprolactin drug completely suppressed the formation of all palpable mammary tumors at a DMBA dose of 5 mg in rats on either LF or HF diets. At a dosage level of 10 mg DMBA, not only was the tumor incidence decreased by the antiprolactin drug but the differential effect of dietary fat was abolished. The data from

this study suggest that enhancement of mammary tumor growth, induced by high dietary fat, may be mediated through alterations in circulating levels of prolactin.

- 2463 1-CARBAMYL-2-PHENYLHYDRAZINE TUMORIGENESIS IN SWISS MICE. MORPHOLOGY OF LUNG ADENOMAS. (E.) Toth, B. (U. Nebraska Med. Ctr., Omaha) and H. Shimizu. *J Natl Cancer Inst* 52(1):241-251, 1974.

A solution of 0.25% 1-carbamyl-2-phenylhydrazine was administered daily for life in the drinking water of randomly bred male (50) and female (50) Swiss mice. In the treated animals the incidence of lung tumors was 78% in females and 69% in males, whereas the corresponding incidences in the 100 untreated controls were 21 and 23%, resp. Light transmission, and scanning electron microscopic examination of the induced lung lesions revealed adenomas composed of alveolar cells, type B. Ultrastructural characteristics in the cytoplasm included lamellar and osmiophilic bodies, membrane-bound lakelike structures, dense particles, and myelin figures. No virus or virus-like particles were observed. The results proved, for the first time, the tumorigenicity of this substituted hydrazine which is known to possess antipyretic action.

- 2464 COLORECTAL CARCINOGENESIS. (E.) Burdette, W. J. (U. Texas Med. Sch., Houston). *Cancer* (Suppl) 34(3):872-877, 1974.

The carcinogens known to induce colorectal neoplasms are discussed along with other factors known to play a role in the pathogenesis of colorectal cancer. The substances include dietary constituents such as bracken fern and aflatoxin B₁; carcinogens, such as *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine, which act directly on the rectal epithelium; and substances requiring metabolic activation such as the aminobiphenyls and nitrosamides, 1,2-dimethylhydrazine, cycasin, and 2',3-dimethyl-4-aminobiphenyl (DMAB). Studies on migrant populations have indicated that genetic and environmental factors play a role in colorectal carcinogenesis. Patients with multiple polyposis or Gardner syndrome and relatives of patients with colorectal carcinoma all have an increased risk for the disease. The mechanism of colorectal carcinoma induction in rats following feeding or injection of 1,2-dimethylhydrazine after birth involves conversion to azomethane and azoxymethane by the liver followed by excretion of the hydroxylated β -glucuronide conjugate of azoxymethane in the bile and conversion into methylazoxymethanol by bacterial flora of the gut. The active methonium ion produced by alkylation of azoxymethanol may be the ultimate carcinogen. Cycasin, found in cycad meal eaten by natives of Guam and Africa, produces colonic adenocarcinomas after conversion to the aglycone methylazoxymethanol by gut flora. DMAB in rats probably also undergoes hydroxylation in the liver and excretion in conjugated form in the bile where it may be converted to the sulfate ester by gut flora. Orthohydroxylamine may be the ultimate carcinogen. In

addition, diets low in fiber content and high in beef, legumes, unrefined carbohydrate and/or fat have been proposed from epidemiologic evidence as suspected large bowel carcinogens. The mechanisms for induction of colorectal cancer in laboratory animals by carcinogens that correlate well with human exposure may hopefully provide a means of determining which factors interact to induce colorectal adenocarcinoma.

- 2465 STUDIES ON PLASMA MEMBRANES. XXI. INHIBITION OF LIVER PLASMA MEMBRANE ENZYMES BY TUMOUR-PROMOTING PHORBOL-12-13-ACETATE (TPA) AND CYTOCHALASIN B. (E.) Bos, C. J. (Dept. Biochem., Antoni van Leeuwenhoek-Huis, Netherlands Cancer Inst., Amsterdam) and P. Emmelot. *Chem Biol Interact* 8(5):349-361, 1974.

Rat liver plasma membranes were used to determine whether the tumor-promoting phorbol-12-13-acetate (TPA) interacts directly with the cell surface in its induction of DNA synthesis and mitosis. Mg²⁺- and Ca²⁺-ATPases, (Na⁺-K⁺)ATPase, 5'-nucleotidase, adenylate cyclase, and cyclic-AMP were chosen as potential enzymatic targets. TPA inhibited the Mg²⁺, Ca²⁺, and (Na⁺-K⁺)ATPases of the rat-liver membranes. A nonpromoting phorbol ester derivative (4-O-methylphorbol-12-13-didecanoate) was without effect. Cholic acid and/or vinblastine (up to 5 x 10⁻³M and 10⁻⁴M, resp.) inhibited the (Na⁺-K⁺)ATPase, glucagon-stimulated adenylate cyclase, and cyclic adenosine-3,5-monophosphate (c-AMP) phosphodiesterase, but had no significant effect on the Mg²⁺- or Ca²⁺-ATPase. Cytochalasin B (4 x 10⁻⁵M) inhibited the (Na⁺-K⁺)ATPase. Thus, these drugs appear to interact directly with the plasma membrane. Their effect may be due to membrane expansion resulting from insertion of the drug between membrane components or drug interaction with a particular protein.

- 2466 BACTERIA AND THE ETIOLOGY OF COLONIC CANCER. (E.) Hill, M. J. (Bact. Metab. Res. Lab., London, England). *Cancer* (Suppl) 34(3):815-818, 1974.

It is postulated that intestinal bacterial flora produce colonic carcinogens or cocarcinogens from bile acids, the concentrations of which are ultimately influenced by the amount of intake of dietary fat. In support of this hypothesis is the fact that full aromatization of the bile acid nucleus yields a cyclopentophenanthrene which has been shown to be carcinogenic. All four types of nuclear dehydrogenation reactions necessary to achieve full aromatization of bile acids have been demonstrated using human gut bacteria and three of these reactions are carried out almost exclusively by a group of clostridia related to *Clostridium paraputrificum* (NDH (nuclear dehydrogenating) clostridia). Analysis of nine world populations differing in their incidence of colonic carcinoma showed a positive correlation between a high cancer rate and fecal bile acid concentration, the degree of bile acid degradation, fecal neutral steroid concentration and degradation, the presence of

intestinal flora capable of aromatizing bile, total fecal acid steroid concentration, and fecal dihydroxycholeic acid concentration. Higher income groups within a given population showed both increased colonic cancer rates and increased fecal acid steroid degradation compared to lower income groups. Eighteen of 22 large bowel carcinoma patients had both more than 6 mg/g dry wt bile acids and more than 10^3 NDH clostridia/g wet wt of feces compared to only one of 51 controls with intestinal diseases other than cancer.

- 2467 CELLULAR INJURY AND CARCINOGENESIS. EVIDENCE FOR THE ALKYLATION OF RAT LIVER NUCLEIC ACIDS *IN VIVO* BY N-NITROSOMORPHOLINE. (E.) Stewart, B. W. (Middlesex Hosp. Med. Sch., London, England), P. F. Swann, J. W. Holsman and P. N. Magee. *Z Krebsforsch* 82(1):1-12, 1974.

An i.p. dose of nitrosomorpholine (400 mg/kg) became rapidly distributed throughout the tissues of female Wistar rats. The concentration in the tissue fell to less than 10% of the initial value within 18 hr of injection. After administration of the same dose of $3\text{-}^{14}\text{C}$ -nitrosomorpholine, 3.3% of the radioactivity was exhaled as $^{14}\text{CO}_2$ over a 24-hr period and 81% was excreted in the urine; 24% of the dose was excreted in the urine as unchanged nitrosomorpholine and 15% as a compound tentatively identified by its chromatographic behavior as nitrosodiethanolamine. Evidence was found for the conversion *in vivo* of nitrosomorpholine to chemically active compounds capable of reacting with nucleic acids. An acid hydrolysate of RNA and DNA from the livers of rats given $3\text{-}^{14}\text{C}$ -nitrosomorpholine contained six radioactive compounds which could be separated by chromatography on Dowex 50. One of these compounds appears to be 7-(2-hydroxyethyl)guanine; the others were not identified.

- 2468 ANGIOSARCOMA OF THE LIVER FOLLOWING VINYL CHLORIDE EXPOSURE. (E.) Block, J. B. (Med. Consulting Group, Kentucky Dept. Labor, Frankfort). *JAMA* 229(1):53-54, 1974.

Recently, six workers exposed to vinyl chloride have died of angiosarcoma of the liver. The patients were all men, aged 38-58 yr. They had worked with vinyl chloride 12-28 yr (mean, 18 yr) prior to first hospital admission. Four of the patients had some non-alcoholic form of cirrhosis of the liver, and in three cases the liver neoplasms were first diagnosed as gastric ulcers. In vinyl chloride workers, the serum alkaline phosphatase determination appears to be more sensitive than other serological tests. SGOT levels are also frequently elevated, but this does not occur until late in the course of the disease. Carcinoma of the liver can be cured only by surgical excision of well-localized lesions. Chemotherapeutic agents are of palliative value only and radiation therapy may alleviate symptoms but does not prolong survival. It should be determined whether the development of angiosarcoma of the liver is the result of low-level exposure of vinyl chloride over a period of years or whether the tumor results from high-level exposure many years previously.

- 2469 HYPERPLASTIC NODULES AND ADENOMAS OF EXOCRINE PANCREAS IN AZASERINE-TREATED RATS. (E.) Longnecker, D. S. (Dartmouth Med. Sch., Hanover, N. H.) and B. G. Crawford. *J Natl Cancer Inst* 53(2):573-577, 1974.

Long-term studies of the carcinogenicity of azaserine in Charles River Wistar rats were undertaken to develop a model of adenocarcinoma of the pancreas. Rats were treated for 6 weeks to 6 months with 1 or 2 weekly i.p. azaserine injections. Single doses were 5-25 mg/kg; total doses were 120-300 mg/kg. All of 18 rats autopsied $3\frac{1}{2}$, 6 or 8 months after initiation of treatment had nodular hyperplastic foci in the pancreas, and three rats had small exocrine adenomas. No malignant tumors were found. One of six control rats contained one hyperplastic nodule in exocrine pancreas. The absence of hyperplastic or neoplastic changes in other tissues suggests a specific effect in the pancreas. These lesions are of acinar cell origin, whereas human adenocarcinoma of the pancreas is generally interpreted as ductlike.

- 2470 ENHANCEMENT OF 7,12-DIMETHYLBENZANTHRACENE SKIN CARCINOGENESIS BY ADENOSINE 3',5'-CYCLIC MONOPHOSPHATE. (E.) Curtis, G. L. (U. Nebraska Med. Ctr., Omaha), F. Stenback and W. L. Ryan. *Cancer Res* 34(9):2192-2195, 1974.

Cyclic AMP (100 or 200 μg) was injected i.p. into strain A mice at time of topical application of 7, 12-dimethylbenzanthracene (DMBA, 20 μg twice weekly) on the interscapular area of the skin. After 4 wk of treatment, the mice developed ulcerations at the site of DMBA applications; controls receiving DMBA but not cyclic AMP did not develop ulcerations. At this point, carcinogen treatment was discontinued but the cyclic AMP injections continued for another 30 wk. Cyclic AMP produced a marked increase in the number of tumors (primarily skin papillomas and squamous cell carcinomas) over that occurring in mice treated with DMBA and 0.15 M NaCl. However, it did not alter the latency between the commencement of carcinogen application and the appearance of tumors. 5'-AMP (200 μg), the immediate metabolite of cyclic AMP, did not affect tumor incidence in DMBA-treated mice. Mice treated with 5'-AMP did not develop skin ulcerations, nor did mice treated with 5 μg DMBA and cyclic AMP. The mechanism by which cyclic AMP amplifies the carcinogenic effect of DMBA is not known.

- 2471 SOME STUDIES ON THE METABOLISM *IN VITRO* OF DIMETHYLNITROSAMINE BY RAT LIVER. (E.) Lake, B. G. (British Industrial Biol. Res. Assoc., Carshalton, Surrey, United Kingdom), C. E. Heading, J. C. Phillips, S. D. Gangolli and A. G. Lloyd. *Biochem Soc Trans* 2(4):610-612, 1974.

Whole rat liver homogenates were separated into crude nuclear, mitochondrial, microsomal, and soluble (cell sap) fractions, and the dimethylnitrosamine demethylase activity of each fraction determined. The enzyme activity of the nuclear, mitochondrial, microsomal, and soluble fractions accounted for 2, 3, 46, and 5% of the total activity,

resp.; the postmitochondrial supernatant contained the total activity and, on resuspending the microsomal fraction in the cell sap, all the enzyme activity was restored. Apparent Michaelis constants were 0.32, 1.5, and 35 mM, with corresponding maximal rates of 0.88, 1.8, and 4.8 μmol of formaldehyde formed/hr/g of liver when the kinetics of dimethylnitrosamine demethylase were investigated in the postmitochondrial supernatant. Cytochrome P-450 and perhaps other components of the hepatic microsomal mixed-function-oxidase complex do not appear to be wholly involved in the *in vitro* demethylation of dimethylnitrosamine. Cytochrome p-450 does not appear to be a rate-limiting step in dimethylnitrosamine demethylation, which is probably a multi-component process and not a single-step enzymic oxidative demethylation.

2472 MORPHOLOGICAL CHANGES INDUCED IN MOUSE LIVER BY β -NAPHTHYLAMINE AND α -NAPHTHYLAMINE. (Rus.) Kondrat'eva, A. F. (N. N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR) and S. A. Kalashnikov. *Vopr Onkol* 20(1):103-106, 1974.

Histological studies of liver changes induced by β -naphthylamine (β -NA) were performed on male DBA mice. Experimental animals were given food to which β -NA (2mg/animal) had been added. Control liver samples were taken from intact mice and mice fed the same dose of non-carcinogenic α -naphthylamine (α -NA). After 60-100 feedings of β -NA, bile duct proliferation (microcholangioma) was observed in the liver. Pronounced morphological changes in the liver structure were observed after 300-360 feedings of food containing β -NA. Acute structural changes consisted of diffuse hyperplasia followed by atypia. Neoplastic cells in the liver resemble pluripotent cambium elements, and are believed to be the major cause of liver tumors. A large amount of RNA was observed in the cytoplasm of the liver cell. Parts of the liver tissue had adenoma cells. One animal had adenocystoma. Microcholangioma and adenocystoma are believed to be the result of β -NA action. The α -NA controls exhibited only fatty liver.

2473 ENHANCEMENT OF CHEMICAL CARCINOGEN-INDUCED TRANSFORMATION OF CULTURED SYRIAN HAMSTER CELLS. (E.) Donovan, P. J. (Natl. Cancer Inst., Bethesda, Md.) and J. A. DiPaolo. *Cancer Res* 34(10):2720-2727, 1974.

The effects of caffeine on transformation and survival of cultured fetal Syrian hamster cells treated with benzo(a)pyrene (2.5 $\mu\text{g}/\text{ml}$), *N*-acetoxy-2-fluorenylacetamide AcAAF, (1 $\mu\text{g}/\text{ml}$) or *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) (0.25 $\mu\text{g}/\text{ml}$) were studied. The concentrations of caffeine used (50-200 $\mu\text{g}/\text{ml}$) were nontransforming and nonlethal. Cells treated with caffeine starting 1 hr after addition of carcinogen showed a time- and concentration-dependent increase in cell toxicity as determined by cloning efficiency. Treatment with 50 $\mu\text{g}/\text{ml}$ caffeine for 2 days resulted in a 20-30% reduction in cloning efficiency. Addition of 50 or 100 $\mu\text{g}/\text{ml}$ caffeine 1 hr after carcinogen and lasting for 48 hr increased

the number of transformed colonies by three- to six-fold compared to that seen with carcinogen alone. Caffeine added 1 hr prior to carcinogen did not increase cell toxicity or alter transformation frequency. Addition of caffeine (0.5-200 $\mu\text{g}/\text{ml}$) 1 hr after addition of AcAAF resulted in decreased cloning efficiency and increased transformation frequency with increasing caffeine concentration. Addition of 50 $\mu\text{g}/\text{ml}$ caffeine for 48 hr at different times after addition of carcinogen caused a maximum 10- to 17-fold enhancement of transformation when caffeine was added after 4 hr. Addition of caffeine at later times for periods as short as 12 hr caused no enhancement of AcAAF-induced transformation but did cause a 6-fold MNNG-induced enhancement. Thus, caffeine potentiation of transformation and cell survival depends on its concentration, its time of addition, the length of exposure, and the type of carcinogen. Any possible role that DNA repair mechanisms may play in this process is unknown.

2474 ISOLATION OF THE TUMOR-INDUCING RNA FROM ONCOGENIC AND NONONCOGENIC *AGROBACTERIUM TUMEFACIENS*. (E.) Beljanski, M. (Inst. Pasteur, Paris, France), M. I. Aaron-Da Cunha, M. S. Beljanski, P. Manigault and P. Bourgairel. *Proc Natl Acad Sci USA* 71(5):1585-1589, 1974.

Two RNA fractions were isolated and purified from both oncogenic and nononcogenic strains of *Agrobacterium tumefaciens*. Both RNAs were capable of inducing the formation of transplantable tumors when introduced into wound sites in the stems of *Datura stramonium* plants. One of the RNA fractions was bound to an RNA-directed DNA polymerase, while the other was associated with the bacterial DNA. Physical evidence suggest that both are single stranded and small in size; linear sucrose gradients show that their size corresponds to a value of 5-6 S. A concentration of 4-5 μg of the RNAs dissolved in 0.01 ml of water was effective in initiating the formation of transplantable tumors in *Datura* plants. The results suggest that a specific RNA may play an important role in the tumor cell transformation in the crown gall disease. The tumor-inducing RNA obtained from *A. tumefaciens* could be involved in inducing the tumorous state by being transcribed into DNA by a RNA-directed DNA polymerase-like enzyme; it would then be physically associated with or integrated into and replicate with the genome of the host cell. A second, more likely, alternative is that it may be present in the form of a more or less autonomous entity.

2475 A SENSITIVE METHOD TO MEASURE PHYSICAL AND CHEMICAL CARCINOGEN-INDUCED "UNSCHEDULED DNA SYNTHESIS" IN RAPIDLY DIVIDING EUKARYOTIC CELLS. (E.) Trosko, J. E. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and J. D. Yager. *Exp Cell Res* 88(1):47-55, 1974.

A sensitive assay for quantitating unscheduled DNA synthesis (repair synthesis) in transformed human amnion (AV3) cells was developed. The combined use of hydroxyurea and arginine-deficient culture medium

enables the detection of 10- to 20-fold increases in unscheduled DNA synthesis after treatment with N-acetoxy-2-acetylaminofluorene (N-acetoxy-AAF) or ultraviolet (UV) light. The technique allows the detection of DNA repair synthesis following treatment with extremely low doses of mutagens and carcinogens. Using this technique, the level of unscheduled DNA synthesis was shown to increase with increasing concentrations of N-acetoxy-AAF or increasing doses of UV. The increased level of unscheduled DNA synthesis in the presence of increasing N-acetoxy-AAF concentrations was due to differential rates of repair with differing concentrations. The unscheduled DNA synthesis occurred in the nucleus. The unscheduled DNA synthesis stimulated by UV and N-acetoxy-AAF can be detected with both ^3H -TdR and ^3H -GdR precursors. DNA repair initially occurs at a high rate, the rate gradually decreasing with time.

- 2476 THE *IN VIVO* FORMATION AND TURNOVER OF S-ADENOSYLMETHIONINE FROM METHIONINE IN THE LIVER OF NORMAL RATS, OF ANIMALS FED DIMETHYLNITROSAMINE, AND OF PARTIALLY HEPATECTOMISED ANIMALS. (E.) Craddock, V. M. (MRC Labs., Carshalton, Surrey, England). *Biochem Pharmacol* 23(17):2452-2454, 1974.

The formation and turnover of S-adenosylmethionine (SAM) during carcinogenesis and the specific activity of SAM in regenerating liver at different times after administration of ^{14}C -methionine was studied. The turnover of SAM in the livers of female rats fed a diet containing dimethylnitrosamine (50 ppm) for 18 weeks was similar to the normal rate. There was no significant alteration in the rate or extent of labeling of SAM. It is the specific activity of SAM which is relevant in interpretation of measurements of methylation of RNA and DNA in normal and precancerous animals. Alterations in, for example, the pool size of methionine, or in the blood supply to the premalignant liver, would affect the level of macromolecular methylation only indirectly via an effect on the synthesis of SAM. Therefore, as a change in the labeling of SAM is considered not to be responsible for the increased labeling of t-RNA which had been found to occur in precancerous liver after injection of ^{14}C -methionine, this increase in labeling is thought to represent an actual increase in the extent of methylation of t-RNA.

- 2477 DIFFERENTIAL TOXICITY OF TOBACCO SMOKE TO VARIOUS CELL TYPES INCLUDING THOSE OF THE IMMUNE SYSTEM. (E.) Holt, P. G. (U. Western Australia, Perth Med. Ctr., Shenton Pk.), W. N. Bartholomaeus and D. Keast. *Aust J Exp Biol Med Sci* 52(2):211-214, 1974.

Monolayer cultures of C57 Black mouse fibroblasts, epithelioid cells, peritoneal and alveolar macrophages, and spleen lymphocytes and human fetal skin, tongue, and lung fibroblasts were exposed in inhalation chambers to a standard dosage of fresh tobacco smoke. Cells of the immune series (lymphocytes, peritoneal and alveolar macrophages) exhibited a greater susceptibility to the immediate toxic effects of the smoke than did the fibroblasts or epithelioid cells.

Mast cells from peritoneal macrophages were particularly susceptible to the toxic effects of cigarette smoke, 72% exhibiting degranulation 30 min after exposure. Mast cells exposed to aqueous solutions of tobacco smoke for 24 hr showed significant degranulation, even at a tobacco smoke extract dilution of 1 in 200. The data suggest that the mechanism involved in the increased susceptibility to respiratory infections and tumor development in smokers may involve the depression of local immunity as a result of damage to cells of the immune series in the lung.

- 2478 EFFECT OF INTRATUMOR INJECTION OF LIVE BCG ON 3-METHYLCHOLANTHRENE-INDUCED TUMORS OF PRIMARY AND EARLY TRANSPLANT GENERATIONS IN MICE. (E.) Tanaka, T. (Natl. Cancer Ctr. Res. Inst., Tokyo, Japan). *Cann* 65(2):145-151, 1974.

The effect of intratumor injections of *Bacillus Calmette-Guerin* (BCG) was examined in primary tumors induced by 3-methylcholanthrene and early transplant generations of syngeneic tumors in a group of SWM/Ms mice previously injected with BCG and in noninjected mice. Intratumor injection of BCG (3×10^7 or 10^8) into the third generation of 3-methylcholanthrene-induced growing tumors led to regression of tumor growth in six of 32 mice (19%) and induced systemic tumor immunity in 5 of these 6 mice. Intratumor injection of BCG ($2 \times 10^7/0.1$ ml) in primary tumors led to tumor retardation in three of 22 mice (14%) with tumor nodules of 3-10 mm in diameter. The survival period of animals treated with BCG was longer than those of saline-treated controls.

- 2479 ASSESSMENT OF THE CARCINOGENICITY AND MUTAGENICITY OF CHEMICALS. (E.) World Health Organization Scientific Group (Geneva, Switzerland). *World Health Organization Technical Report Series*, No. 546, 19p., 1974.

Recognizing that the possible mutagenic or carcinogenic action of some food chemicals poses a definite human health hazard, a Scientific Group on the Evaluation of Testing of Drugs for Mutagenicity was convened by the World Health Organization (WHO) in 1971 to discuss an evaluation of risks. Emphasis was placed on methods of testing and the interpretation of results. The Group's report discusses mechanisms of mutagenesis and carcinogenesis, the relationship between mutagenesis and carcinogenesis, mutagenicity and carcinogenicity tests, the possibility of threshold dose levels in mutagenesis and carcinogenesis, and assessment of hazards. Based on conclusions drawn from the discussion, it is recommended that: WHO promote the development of approaches and procedures for assessing the risks of low-level carcinogen exposure by extrapolation from experimental bioassay data; WHO promote more research into methods for the detection of carcinogens and coordinate and support international monitoring of the levels of some of these chemicals; and WHO convene a meeting to discuss the assessment of risks associated with different levels of unavoidable exposure. WHO should also encourage more

basic research into mechanisms of carcinogenesis, further studies on the effects of compounds having hormone-like actions, pathological examinations in studies of carcinogenesis, design of a practicable test for point mutations in mammalian systems, and additional research into the association of mutagenicity and carcinogenicity. A proposed procedure for the assessment of health hazards of carcinogens at very low levels of exposure is appended.

- 2480 CHARACTERISTICS OF RAT NORMAL MAMMARY EPITHELIAL CELLS AND DIMETHYLBENZANTHRACENE-INDUCED MAMMARY ADENOCARCINOMA CELLS GROWN IN MONOLAYER CULTURE. (E.) Cohen, L. A. (Naylor Dana Inst. Dis. Prevention, Am. Health Fdn., New York, N.Y.). *In Vitro* 10(1/2):51-62, 1974.

Normal mammary epithelial cells (RBE cells) and 7,12-dimethylbenz(a)anthracene (DMBA)-induced adenocarcinoma cells (RBA cells), both derived from female Sprague-Dawley rats, were grown in monolayer culture. The RBE and RBA cells differed from each other in terms of morphology and cell-to-cell relationships. Compared with the RBE cells, the RBA cells demonstrated a shorter population doubling time, a greater terminal cell density, and a higher cloning efficiency. Among the RBE cells, departure from the diploid chromosome number never exceeded more than a single pair deletion; no polyploidy was observed. The RBA cells exhibited a variety of chromosome numbers, ranging from 51 to 77; an increase in small metacentrics typified the RBA chromosomal pattern. Unlike the RBE cells, the agglutinability of the RBA cells in the presence of concanavalin A and wheat germ agglutinin was dose-dependent and specific for the respective monosaccharide haptens. The two cell types also differed in their response to trypsin. Unlike the RBA cells, the RBE cells were sensitive to the toxic effect of DMBA and were unable to grow in soft agar or to form tumors when inoculated into newborn isologous rats.

- 2481 SYNERGISTIC ACTION OF PHORBOL ESTERS IN MITOGEN-ACTIVATED BOVINE LYMPHOCYTES. (E.) Mastro, A. M. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and G. C. Mueller. *Exp Cell Res* 88(1):40-46, 1974.

The action of phorbol esters in cultures of bovine lymphocytes treated with concanavalin A (Con A) or phytohemagglutinin-P (PHA) was studied. Lymphocytes from bovine retropharyngeal lymph nodes were stimulated by PHA and Con A to differentiate into blast cells and to engage in DNA synthesis within 48-60 hr. Phorbol myristate acetate (PMA) increased the rate of DNA synthesis at 48-50 hr, but had little effect at 60-72 hr. PMA stimulated a certain population of cells which would not ordinarily respond to replicate in the presence of PHA or Con A. PMA alone had little or no effect on the rate of DNA synthesis. While a PMA-induced enhancement of DNA synthesis was seen when the ester was added at the same time as PHA or Con A, no enhancement was seen

when the addition of PMA was delayed 8 or 24 hr. The rate of DNA synthesis was increased when Con A was added to cultures preincubated with PMA. Phorbol diacetate (PdiC2) also enhanced DNA synthesis when added with PHA or Con A, but did not increase the rate of synthesis in the absence of lectin. PMA was equally effective in stimulating DNA synthesis in lectin-treated cultures of syngeneic and mixed lymphocytes. When PMA was added to cells immediately after their isolation from the animal, instead of after overnight preincubation, a significant stimulation of DNA synthesis was observed at 48 hr in the absence of lectin; the capacity of the cultures to respond to PMA as the sole mitogen disappeared with preincubation of the cells for 16 hr. A change of the medium after preincubation did not restore the cells' ability to respond to PMA alone. PMA may act synergistically with some natural mitogen associated with the freshly isolated cells to induce lymphocyte replication. The data indicate that phorbol esters influence cellular processes that regulate the efficiency of endogenous or exogenous mitogens.

- 2482 COMPARISON OF THE O-DEALKYLATION OF 7-ETHOXYCOUMARIN AND THE HYDROXYLATION OF BENZO[a]PYRENE IN HUMAN PLACENTA. EFFECT OF CIGARETTE SMOKING. (E.) Jacobson, M. (Hoffmann-LaRoche, Inc., Nutley, N.J.), W. Levin, P. J. Poppers, A. W. Wood and A. H. Conney. *Clin Pharmacol Ther* 16(4):701-710, 1974.

A method is described for measuring the *in vitro* metabolism of 7-ethoxycoumarin or coumarin to 7-hydroxycoumarin. This method was used to measure the O-dealkylation of 7-ethoxycoumarin and the hydroxylation of coumarin by placentas from 12 nonsmokers and from 12 women who smoked cigarettes. Although an induced level of benzo[a]pyrene (BP) hydroxylase activity was found in each placenta obtained from women who smoked cigarettes during pregnancy, 7-ethoxycoumarin O-dealkylase activity was induced (about 2-fold) only in placentas whose BP hydroxylase activity was markedly induced (50- to 100-fold). These results indicate that ethoxycoumarin dealkylase activity parallels BP hydroxylase activity in human placenta only in individuals with markedly induced BP hydroxylase activity. No detectable hydroxylation of coumarin in the 7-position was observed in placental homogenates from nonsmokers or from women who smoked cigarettes.

- 2483 EFFECTS OF CARCINOGENS AND OTHER AGENTS ON HISTONE METHYLATION BY A HISTONE ARGININE METHYLTRANSFERASE PURIFIED FROM RAT LIVER CYTOPLASM. (E.) Baxter, C. S. (U. Florida Coll. Med., Gainesville) and P. Byvoet. *Cancer Res* 34(6):1418-1423, 1974.

The effects of carcinogenic agents and their metabolites were studied *in vitro* on a histone arginine methyltransferase enzyme purified from male Holzman rat liver cytoplasm. This enzyme shows several properties similar to those reported for tRNA methyltransferases. Histone methylation was inhibited by

N-hydroxy-2-aminofluorene, *N*-hydroxy-2-acetylaminofluorene, and *N*-acetoxy-2-acetylaminofluorene, the degree of inhibition correlating with the degree of carcinogenicity. The histone arginine methyltransferase had a K_m (4.4 μM) similar to that of the tRNA methyltransferase and, like it, was subject to product inhibition by *S*-adenosyl-L-homocysteine. The histone arginine methyltransferase also showed susceptibility to inhibition by adenine and the adenosine analogs tubercidin and *N*-6-(Δ^2 -isopentanyl) adenosine. The DNA-binding dyes ethidium bromide and acridine orange also inhibited the methyltransferase system. These observations support the proposition that a correlation exists between malfunction in normal histone methylation and induction of neoplasia.

- 2484 CARCINOGENIC AND COCARCINOGENIC ACTIVITY OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) ON MOUSE SKIN. (Fr.) Chouroulinkov, I. (Sci. Res. Inst. Cancer, Villejuif, France) and P. Lazar. *C R Acad Sci [D] (Paris)* 278(23):3027-3030, 1974.

The carcinogenic and cocarcinogenic activity of 12-O-tetradecanoylphorbol-13-acetate (TPA), a well-known promoter, was studied in CD1 (Charles River) mice whose skin was treated with 1 μg TPA 2 or 3 times/wk for 15 or 18 months, starting at age 60 days. Another group was initiated by cutaneous application of 100 μg 7,12-dimethylbenz(a)anthracene (DMBA) 7 days before TPA application started. When applied twice a week, TPA caused both benign and malignant skin tumors (papillomas and epitheliomas) in 25% of all mice, while the corresponding rate for the group treated three times/wk was 75%. The skin tumor incidence was highest in the DMBA-treated, and DMBA-initiated and TPA-treated groups. The latency time, shortest in the two latter groups, decreased with increasing frequency of the TPA application in the other groups. Croton oil, used in control groups, was also carcinogenic. The findings indicate the carcinogenic and cocarcinogenic activity of TPA and challenge the existence of "purely promoting" substances in carcinogenesis.

- 2485 SUSCEPTIBILITY OF INBRED RATS TO GASTRIC AND DUODENAL CARCINOMAS INDUCED BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Martin, M. S. (Fac. Med., Dijon, France), F. Martin, E. Justrabo, R. Michiels, H. Bastien and S. Knobel. *J Natl Cancer Inst* 53(3):837-840, 1974.

Male and female randombred Wistar, inbred Lewis, inbred BD IX, inbred BN, and (Lewis X BN) F_1 rats were given *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (NG) (83 mg/liter) in their drinking water continuously for 7 months. Mean survival after the initiation of NG treatment varied from 295 to 439 days, depending on strain and sex. The NG treatment resulted in a high incidence of gastric and duodenal adenocarcinomas and benign hyperplastic lesions in all strains. Gastric carcinomas were more frequent in BN males than in BN females, Lewis males, and Wistar males. Intestinal carcinomas were more often seen in Lewis males than in Lewis females or BN males. The carcinogenic effect of NG was limited to the upper diges-

tive tract, but a high incidence of nonmalignant biliary cysts was also observed. The data demonstrate the possibility of inducing gastric and duodenal carcinomas in rats of inbred strains with an incidence at least equal to that obtained in outbred animals. Transplantation and immunologic studies would be facilitated by the induction of NG tumors in inbred animals.

- 2486 CARCINOGENIC ACTIVITY OF ALKYLATING AGENTS. (E.) Van Duuren, B. L. (New York U. Med. Ctr., N.Y.), B. M. Goldschmidt, C. Katz, I. Seidman and J. S. Paul. *J Natl Cancer Inst* 53(3):695-700, 1974.

Seventeen direct-acting alkylating agents and chloroethers were administered topically, s.c., and i.p. to female ICR/Ha Swiss mice. Dimethylcarbamyl chloride, a potent skin carcinogen, induced a high incidence of sarcomas at the site of injection after s.c. or i.p. administration. Four of the other 15 compounds (ethyl bromoacetate, 2,3-dichloro-*p*-dioxane, glycol sulfate, and diethyl- β , γ -epoxypropylphosphonate) injected s.c. induced significantly elevated incidences of sarcomas at the site of injection. Only dimethylcarbamyl chloride and 1,2,4,5,9,10-triepoxydecane also induced carcinomas upon application to the skin. Some of these chemicals are used in the chemical industry and others are frequently employed in the chemical laboratory.

- 2487 CLEAR CELL ADENOCARCINOMA OF THE VAGINA AND CERVIX IN YOUNG FEMALES: ANALYSIS OF 37 TUMORS THAT PERSISTED OR RECURRENT AFTER PRIMARY THERAPY. (E.) Robboy, S. J. (Harvard Med. Sch., Boston, Mass.), A. L. Herbst and R. E. Scully. *Cancer* 34(3):606-614, 1974.

The clinical course, characteristics, and response to treatment of 37 of 154 cases of clear cell adenocarcinoma of the vagina or cervix which persisted or recurred following initial treatment are presented. Persistent/recurrent tumor was seen in 19 of 89 patients (21%) with vaginal carcinoma and 18 of 65 patients (28%) with cervical carcinoma. The patients in whom tumor has reappeared after initial therapy ranged in age from 7-29 yr with 6 (16%) being 12 yr or younger at the time of initial diagnosis. Of 32 cases in which maternal history has been obtained, 26 (82%) took diethylstilbestrol or chemically related nonsteroidal estrogens beginning prior to 18 wk gestation for problem pregnancies. Seventeen tumors were vaginal stage I or cervical stage I or IIA; laparotomy in 13 of these showed pelvic node involvement in 8. The remaining 20 cancers were vaginal stage II-IV or cervical stage IIB-IV. Initial therapy was surgical (ranging from local excision to pelvic exenteration) in 22, radiotherapy alone in 9, chemotherapy alone in 3, and combination radio-chemotherapy in 3. Tumors that were large, close to the resection margin, or penetrated > 3 mm into the vaginal or cervical wall, most frequently persisted or recurred. The first recurrence was seen an average of 17 months (2-48 months) after initial therapy and second recurrences (12 patients) were seen an average

of 9 months (1-21 months) following retreatment. While most (53%) recurrences occurred within the pelvis, 35% occurred in the lungs and/or supraclavicular nodes; this incidence contrasts with recurrent squamous cell carcinoma which rarely involves the lung or supraclavicular nodes. Only two of the 12 patients with second recurrences are alive after 2 yr and both have metastatic disease. Of the 37 patients, 24 died 6-68 months (average, 27 months) after initial treatment (3 yr survival = 23%). Only 6 of 13 patients with recurrent or persistent tumor who are still alive 6-69 months after therapy are clinically free of disease; 5 of these had recurrences limited to the vagina.

2488 CARCINOGENS IN RAT MILK: TRANSFER OF INGESTED DIETHYLNITROSAMINE INTO MILK BY LACTATING RATS. (E.) Schoental, R. (Roy. Vet. Coll., London, England), T. A. Gough and K. S. Webb. *Br J Cancer* 30(3):238-240, 1974.

Two lactating random-bred Wistar-Porton rats were given diethylnitrosamine (DEN) 130 mg/kg by stomach tube) 5 days after parturition. The rats were returned to their offspring 30 minutes later. The pups were killed 2, 4, 6, or 49 hr after being reunited with their mother. Offspring of a third nontreated rat served as controls. Significant concentrations of unchanged free DEN were found in the milk removed from the stomachs of the suckling rats within a few hours after being returned to their mothers. The DEN concentration increased from 5-36 mg/liter between 2-6 hr, none being found after 49 hr. There was no evidence of the presence of free volatile metabolic derivatives of DEN. In a parallel experiment, pups of DEN-treated (several 130 mg/kg doses) females were allowed to survive. They grew and developed in apparent good health until tumors appeared later in life; the tumors were probably at least partially attributable to the repeated ingestion of unchanged DEN during lactation.

2489 EXPERIMENTALLY INDUCED CANCER OF THE COLON. (E.) Deschner, E. E. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.). *Cancer* (Suppl) 34(3): 824-828, 1974.

The induction of colonic carcinoma by 1-2, dimethyl hydrazine (DMH) was studied in 56 female CF₁ mice which received weekly s.c. injections (21 mg/kg). Over 90% of DMH-treated mice developed colonic carcinoma by 186 days of treatment. Atypia began to develop after 38 days. DMH showed a propensity for development of multiple, primarily sessile, lesions especially along the terminal portion of the colon. Staining of tumor sections with Alcian blue-p-*amino* salicylic acid showed a marked reduction in the number of mucous-secreting cells. Autoradiographic studies of sections of normal appearing intestine from ³H-thymidine-injected, DMH-treated animals at various times during tumor induction showed elevation of the mitotic index after 49 days and continuing for 3 wk after which it returned to pre-elevated levels. This corresponded with the time of rapid increase in the frequency of focal atypias and immediately preceded the appearance of increasing

numbers of labeled intestinal epithelial cells. The percentage of labeled cells within areas of atypias were often two to three times greater than that of the normal surrounding mucosa. The response within the group of treated animals was highly variable, suggesting that multiple factors (e.g., genetic, physiologic, unknown) play a role in the induction of colonic cancer.

2490 FORMATION OF N-NITROSOPYRROLIDINE IN A DOG'S STOMACH. (E.) Mysliwy, T. S. (Dept. Nutrition Food Sci., Massachusetts Inst. Technol., Cambridge), E. L. Wick, M. C. Archer, R. C. Shank and P. M. Newberne. *Br J Cancer* 30(3):279-283, 1974.

Four dogs were prepared with "indwelling" gastric fistulae, through which was administered 50 ml of an aqueous solution containing sodium nitrate and pyrrolidine. Samples of the gastric contents were obtained at various intervals thereafter and analyzed using combined gas chromatography-mass spectrometry. Over a 30-min period after the administration of the solution, the pH of the stomach contents decreased, the nitrite concentration decreased, and nitrosopyrrolidine was synthesized (first identified after 1 min), rising to a maximum concentration of 0.12-0.96 parts/10⁶. The nitrosopyrrolidine concentration then rapidly declined, probably due to absorption. In the dog's stomach, the rate of formation of nitrosopyrrolidine is subject to pronounced catalytic effects. More information on precursor concentrations in normal diets is needed before a realistic appraisal of the human health hazard posed by *in vivo* nitrosation can be made.

2491 KINETICS OF UPTAKE OF 2-DEOXY-D-GLUCOSE AND 2-AMINOISOBUTYRIC ACID IN CHEMICALLY TRANSFORMED CELLS. (E.) Kuroki, T. (Inst. Med. Sci., Univ. Tokyo, Japan) and S. Yamakawa. *Int J Cancer* 13(2):240-245, 1974.

Kinetics of 2-deoxy-D-glucose and 2-aminoisobutyric acid transport in a series of chemically transformed hamster embryo cells and BALB 3T3 cells were investigated. Maximum velocity of the glucose uptake in chemically transformed cells increased 1.5 to 2.8-fold over controls with no detectable change in apparent Km. Km values were 2.0 mM for hamster embryo cells and 1.25 mM for BALB 3T3 cells. Comparable results were obtained with transformed SV 3T3 cells, which showed increased V_{max} without change in Km. Uptake of 2-aminoisobutyric acid caused little change in V_{max} and the Km was similar despite chemical transformation. Little difference was noted in hexokinase activity between chemically transformed cells and their untransformed counterparts. It is suggested that glucokinase is not present in these cell lines. Transport, rather than post-transport phosphorylation, may be responsible for the increased uptake of glucose after chemical transformation. The increased uptake of nutrients may be the first step in a series of metabolic reactions which modulate the glucose utilization of these cells and also cell response to growth regulators.

- 2492 ROLE OF PODOPHYLLOTOXIN IN THE BEDDING AND DIETARY ZEARELENONE ON INCIDENCE OF SPONTANEOUS TUMORS IN LABORATORY ANIMALS. (E.) Schoental, R. (Roy. Vet. Coll., London, England). *Cancer Res* 34(9):2419-2420, 1974.

C3H^{Vy}FB mice, which have a very high incidence of "spontaneous" mammary and hepatic tumors in the NIH laboratories in the United States, develop fewer tumors when imported to Australia. Among subsequent generations bred in the new environment, the incidence is almost zero. However, the NIH level was restored when the Australian bedding and diet were replaced by the NIH bedding and diet. With regard to bedding, shaving from red cedar wood, *Juniperus virginiana* L., is specifically implicated. The lignan podophyllotoxin may contribute to the carcinogenic action of this bedding. Podophyllin, of which podophyllotoxin is the active constituent, is a mitotic poison, can cause striking hyperplastic lesions, and has caused an increased tumor incidence when fed to mice. With regard to the NIH diet, natural estrogens and, in particular, zearelenone and its congeners, may have carcinogenic action.

- 2493 TRAPPING OF BENZO(a)PYRENE BY BOVINE SERUM ALBUMIN. (E.) Bothorel, P. (Paul Pascal Res. Ctr., Domaine U., Talence, France) and J. P. Desmazes. *Biochim Biophys Acta* 365(1):181-192, 1974.

The trapping of benzo(a)pyrene (BP) by bovine serum albumin was studied *in vitro*. Results of 55 experiments with ³H- or ¹⁴C-BP showed that when BP is shaken with bovine serum albumin solution, only a very small hydrocarbon fraction is bound to the protein (0.063 mole/mole). However, when the two substances are shaken in the presence of 2-chloroethanol-water, a binary transient solvent, more than 10 hydrocarbon molecules are trapped/albumin molecule. The results are the same when defatted bovine serum is used. The ability of 2-chloroethanol to increase the helical percentage in the protein from 45% to 61% may allow BP molecules to reach an internal binding site. Electrophoretic studies show that the albumin is not modified by treatment. UV absorption spectral studies confirmed by results from fluorescence spectral studies are consistent with the existence of two binding sites on the albumin molecule, one on the surface and another inside the protein. BP and bovine serum albumin are not covalently bound.

- 2494 TRACE ELEMENTS IN NORMAL AND MALIGNANT HUMAN BREAST TISSUE. (E.) Schwartz, A. E. (Mount Sinai Sch. Med., New York, N.Y.), G. W. Leddicotte, R. W. Fink and E. W. Friedman. *Surgery* 76(2):325-329, 1974.

Normal and malignant breast tissue from nine patients undergoing radical mastectomy was analyzed for concentrations of trace metals by neutron activation analysis. The mean level of potassium was 8 times greater in the malignant tissue than the normal tissue, the mean phosphorus concentration in the malignant tissue was 11.4 times greater than in the normal tissue, the mean copper level was 2.3 times higher

in the malignant tissue, the mean magnesium concentration was 8 times greater, the mean zinc concentration was 5.7 times greater, and the mean iron concentration was 2.4 times greater. Although these results were not significantly affected by the preservation and transportation of specimens in formalin, freeze-drying offers greater accuracy for future studies.

- 2495 SEA URCHIN EGG DEVELOPMENT UNDER THE ACTION OF BENZO(a)PYRENE AND 7,12-DIMETHYLBENZ(a)ANTHROCENE. (E.) De Angelis, E. (Inst. Cancer Res., Naples, Italy) and G. G. Giordano. *Cancer Res* 34(6):1275-1280, 1974.

The effects of benzo(a)pyrene (BP) and 7,12-dimethylbenz(a)anthracene (DMBA) were studied on the development and differentiation of sea urchin eggs and embryos *in vitro*. Final concentrations of BP and DMBA ranged from 10⁻⁴ to 10⁻⁷M. BP had no effect on sea urchin egg cleavage or differentiation. When added before the first cleavage, DMBA had no effect until after the blastula stage when it showed the specific ability to interfere with mesenchyme cell organization, resulting in abnormal skeletal development in all embryos. BP or DMBA added to ova and sperm for 2-5 hr prior to fertilization failed to affect development of the zygotes. Autoradiographic studies of ³H-BP and ³H-DMBA labeled zygotes showed a greater concentration of DMBA than BP in the nuclei and surface membranes.

- 2496 POLYCYCLIC HYDROCARBON EPOXIDES: THE INVOLVEMENT OF 8,9-DIHYDRO-8,9-DIHYDROXYBENZ(a)ANTHRACENE 10,11-OXIDE IN REACTIONS WITH THE DNA OF BENZ(a)ANTHRACENE-TREATED HAMSTER EMBRYO CELLS. (E.) Swaisland, A. J. (Inst. Cancer Res., London, England), A. Hewer, K. Pal, G. R. Keysell, J. Booth, P. L. Grover and P. Sims. *FEBS Lett* 47(1):34-38, 1974.

Hamster embryo cells were incubated for 24 hr with ³H-benz(a)anthracene (2 µg/ml) in dimethylsulfoxide and the DNA (aDNA) isolated and purified. In a second experiment, deproteinized salmon sperm DNA (bDNA) was mixed with a rat-liver microsomal preparation and incubated for 30 min with ³H-8,9-dihydro-8,9-dihydroxybenz(a)anthracene. The hydrolysates of the bDNA gave elution profiles on Sephadex LH20 column chromatography which indicated the presence of a radioactive product in a position similar to that occupied by the product obtained from the aDNA. bDNA products were not formed in microsomal incubations which lacked the cofactors necessary for the monooxygenase. Thus, further metabolism of the 8,9-diol of benz(a)anthracene may be involved in the reactions with DNA which occur following treatment with benz(a)anthracene. Metabolic oxidation of the isolated 10,11 double bond in the 8,9-diol was indicated. In reactions with DNA, 8,9-dihydro-8,9-dihydroxybenz(a)anthracene 10,11-oxide and the microsomal metabolite of 8,9-dihydro-8,9-dihydroxybenz(a)anthracene yielded products which were identical chromatographically to those formed in cells treated with benz(a)anthracene. The data support

the concept that epoxides are the activated intermediates which are metabolically formed from polycyclic hydrocarbons and which react with cellular nucleic acids.

- 2497 THE EFFECT OF BENZO(a)PYRENE DOSE ON THE HISTOLOGICAL STRUCTURE OF EXPERIMENTAL LUNG CANCER. (Rus.) Ianisheva, N. Ia. (Kiev Sci. Res. Inst. Gen. Communal Hyg., USSR) and N. V. Balenko. *Gig Sanit* (8):14-17, 1974.
- Studies were carried out on 460 rats exposed to 0.005 - 25 mg of benzo(a)pyrene administered intratracheally once a month for 10 months. Animals receiving the doses of 0.5, 2.5, and 25 mg had lung tumors in proportions of 28.2, 42.8 and 80% resp. of the total number of tumors involved. Malignant tumors were found in corresponding proportions of 15.7, 28.5 and 42.5%, resp. The most common types of malignant tumors were squamous cell keratinized carcinoma, mixed glandular and squamous cell carcinoma, and unidentified oat cell carcinoma. The maximum dose of 25 mg induced squamous cell carcinoma of the lung in 53.8% of the animals; adenocarcinoma, in 27.1%; adenocarcinoid, in 15.3%, unidentified tumors, in 7.68%.
- 2498 DATA FOR HYGIENIC STANDARDS FOR THE CARCINOGEN, DINITROSODIMETHYLETHYLENE DIAMINE. (Rus.) Litvinov, N. N. (No affiliation), V. N. Kurylev and E. R. Grushin. *Gig Sanit* (9):80-84, 1974.
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- 2500 MORPHOLOGICAL AND BIOCHEMICAL EFFECTS OF 1,2-DIMETHYLHYDRAZINE AND 1-METHYLHYDRAZINE IN RATS AND MICE. (E.) Hawks, A. (Middlesex Hosp. Med. Sch., London, England), R. M. Hicks, J. W. Holtsman and P. N. Magee. *Br J Cancer* 30(5):429-439, 1974.
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- 2505 ERYTHROID COLONY FORMATION *IN VITRO* BY DIMETHYLSULFOXIDE-TREATED ERYTHROLEUKEMIC CELLS. (E.) Goldstein, K. (Mount Sinai Sch. Med., City U. New York, N.Y.), H. D. Preisler, J. D. Lutten and E. D. Zanjani. *Blood* 44(6):831-836, 1974.
- 2506 EFFECTS OF ⁶⁰CO GAMMA IRRADIATION ON AFLATOXIN B₁ AND B₂ PRODUCTION BY *ASPERGILLUS FLAVUS*. (E.) Applegate, K. L. (Dept. Poultry Sci., Ohio State U., Columbus) and J. R. Chipley. *Mycologia* 46(3):436-445, 1974.
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- 2550 EFFECT OF STERCULIC ACID UPON AFLATOXICOSIS IN RATS FED DIETS CONTAINING SATURATED AND UNSATURATED FAT. (E.) Wells, P. (Sch. Pub. Hlth., U. California, Los Angeles), L. Aftergood and R. B. Alfin-Slater. *J Am Oil Chem Soc* 51(10):456-460, 1974.
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- See also:
- * (Rev): 2402, 2422, 2426, 2430, 2433, 2441, 2442
 - * (Phys): 2553, 2555
 - * (Viral): 2627, 2632
 - * (Immun): 2690, 2698, 2701, 2703, 2709, 2734, 2738, 2754, 2760, 2767, 2771
 - * (Path): 2791
 - * (Epid-Biom): 2833, 2836, 2840, 2842, 2843, 2844, 2845, 2847

22553 TUMOURS DEVELOPED IN PEOPLE INJECTED WITH THORIUM DIOXIDE (THOROTRAST) (PORTUGUESE EXPERIENCE). (E.) da Silva Horta, J. (Dept. Pathol., Fac. Med., Lisbon, Portugal). *Proc Third Int Meet Toxic Thorotrast (Copenhagen) April 25-27, 1973* pp. 223-245.

A total of 90 biopsies, 210 autopsies, and 12 splenectomies have been performed on Portuguese patients injected with Thorotrast. Fifteen cases of liver hemangioendotheliomas were found, along with one hemangioendothelioma of the bone marrow, one reticulosarcoma of the liver, spleen, and bone marrow, nine cholangiocarcinomas, two hepatomas, and five tumors (two spindle cell sarcomas on the edge of a cervical granuloma, two cholangiocarcinoma at the edge of liver granulomas, and one adenocarcinoma of the common hepatic bile duct on the edge of a postportography granuloma) on the edge of large Thorotrast deposits. There were also two cases of bone sarcomas, neither of which was histologically confirmed. The genesis of the various Thorotrast tumors is discussed.

22554 THE EFFECT OF THOROTRAST ENRICHED WITH Th^{230} . (E.) Faber, M. (Finsen Lab., Finsen Inst., Copenhagen, Denmark). *Proc Third Int Meet Toxic Thorotrast (Copenhagen) April 25-27, 1973* pp. 294-302.

Rabbits were injected with 10 ml of depleted Thorotrast²³² (Th^{232}) (Group 1) 10 ml of Thorotrast enriched with Th^{230} to an α -activity 7 or 49 times normal (Groups 2 and 3) or 10 ml of fresh commercial Thorotrast (Group 4). The Group 3 animals died during the first yr from liver insufficiency with histological evidence of a radiation produced liver cirrhosis. The mean age at death from tumors (hemangioendotheliomas) in Group 2 was 103 days, and in those injected with depleted Thorotrast, the corresponding age was 147 days. The mean age at death from tumors in the animals given fresh commercial Thorotrast was 126 days. In another experiment, 0.3 ml of the Th^{230} -enriched Thorotrast injected into Group 3 was injected into another group of rabbits. The mean time between injection and death from tumor was 249 wk. The data indicate the significance of the Thorotrast-associated radiation in the production of hemangioendotheliomas in rabbits.

22555 THE STABILITY OF LEUKOMOGENIC RISK IN HUMAN MARROW IRRADIATED BY α RAYS. (E.) Marinelli, L. D. (Ctr. Human Radiobiol., Argonne Natl. Lab., Ill.). *Proc Third Int Meet Toxic Thorotrast (Copenhagen) April 25-27, 1973* pp. 303-307.

The permanence of a leukemogenic risk induced by high LET radiation delivered at low dose rates was tested by studying the latent period of leukemias and the corresponding man-yr at risk in the Thorotrast-injected patients of Denmark. The influence of dose rate and total dose was strongly suggested by two observations: the known average dose in-

jected in leukemia cases was definitely higher (34.4 cc) than the average of all injections; (23.3 cc) and irrespective of the average time at risk, the incidence of leukemia increased with dose. These figures, although not individually significant, are indicative of a trend. The data indicate that, contrary to evidence for low LET radiation at high dose rates, the leukemogenic risk induced by α -radiation delivered at low dose rates appears to be constant for intervals ranging up to more than 20 yr postinjection. This is in accord with general radiobiological findings that there is little or no recovery from the effects produced by high LET radiation.

22556 DOSE EFFECT RELATIONS IN HEPATIC CARCINOGENESIS. (E.) Faber, M. (Finsen Lab., Finsen Inst., Copenhagen, Denmark). *Proc Thira Int Meet Toxic Thorotrast (Copenhagen) April 25-27, 1973* pp. 308-316.

The effect of increasing doses of Thorotrast on the risk of tumor development was studied among Thorotrast-injected patients. Only the cumulative doses in the liver were considered. The cumulative dose in the liver was lowest among patients dying from nonmalignant diseases, somewhat higher among those dying from non-Thorotrast malignancies, and higher still among those dying from Thorotrast malignancies. Among the latter group, the highest doses were found among those dying from hemangioendotheliomas. However, the largest doses were found among the surviving Thorotrast-injected persons. The cancer risk among Thorotrast patients was compared with the risk as a dose-effect relationship based on data for other types of human radiation exposures. The results indicate that the effect of Thorotrast in man is due to the radiation, and that the colloid, although producing serious histological effects, is reasonably inert with respect to carcinogenicity.

22557 EXPECTED LATE EFFECTS IN THOROTRAST PATIENTS. (E.) Muth, H. (Inst. Biophys., U. Saarlandes, Homburg, Germany), E. Oberhausen, R. Kunkel and U. Herzfeld. *Proc Third Int Meet Toxic Thorotrast (Copenhagen) April 25-27, 1973* pp. 320-333.

Biophysical examinations were carried out on 534 patients who had been injected with an average of 15 ml of Thorotrast. Measurements were made of the total body radioactivity and the thoron concentration in the exhaled air. Taking into account the results of special animal experiments and using the results of the direct measurements on patients, the dose rate was calculated as a function of the age of the thorotrast burden; the accumulated radiation dose in different organs was also calculated. The radiation doses absorbed from alpha particles over a period of 30 yr after an average (15 ml) and maximum (50 ml) dose of Thorotrast are: 600 rad (average) and 1300 rad (maximum) by the liver; 1400 rad and 3000 rad by the spleen, 280 and 900 rad by the bone marrow, and 20 rad and 70 rad by the skeleton. Thirty yr after a 15 ml injection, the bronchi would be expected to absorb 50 rad, the main bronchi would absorb 230 rad, and the trachea would absorb 370 rad.

Using these data and the most probable values for risk coefficients available, the expected radiation-induced late effects in a thorotrast group would be: no significant increase in bone tumors; a 20% increase in leukemia; and a 16% increase in liver tumors. Recording and first examination of thorotrast patients must be combined with systematic follow-up studies for at least 10 yr to yield optimally useful radiobiological data.

- 2558 NUCLEAR POWER AND PUBLIC HEALTH. (E.)
Anonymous. *Bull Int Atomic Energy Agency*
16(4):46-52, 1974.

The public health effects of nuclear power production can be divided into three categories: accidental injuries and deaths not related to radiation; radiation health effects; and environmental effects. Accidental injuries and deaths are caused by interactions between man and the energy system. They are largely related to occupation, although the general public may be involved in accidents involving the transportation of materials. Radiation health effects include harmful effects observed in exposed individuals, either relatively soon or long after exposure, and genetic effects, which affect subsequent generations. They may result from exposure to radiation or to emitted pollutants during normal operations or as a result of accidents in the energy system; they may affect employees and the general public. Excessive exposure to radiation in uranium mining, for example, results in an increased risk of lung cancer. The main public health concern in the operation of nuclear systems is the exposure of employees of nuclear facilities to radiation, the disposal of radioactive wastes, reactor safety, and the transport of radioactive materials. The exposure of populations near nuclear facilities to radiation is not a major cause of concern. Environmental effects, both good and bad, are caused by physical and chemical interaction between emitted pollutants, including thermal pollution, and the environment.

- 2559 INTERNAL IRRADIATION AND CARCINOGENESIS.
(E.) Gossner, W. (No affiliation). *Curr Top Radiat Res Q* 9:35-39, 1974.

Suitable animal models must be developed for better understanding of the pathogenesis of late radiation-induced lesions in man. The principal known late effect of internal radiation is the induction of tumors. Animal experiments concerned with tumor induction after the incorporation of radionuclides may be used to assess the relative risks of internally deposited isotopes of particular industrial and medical relevance or may be used to analyze the general aspects of carcinogenesis. Ionizing radiation can act as an initiating factor and as a promoting factor. Initiating effects may tend to predominate at low dose levels; these effects may be magnified by promoting effects at intermediate dose levels and not be expressed at high dose levels because of excessive injury. Radiation carcinogenesis can be affected by the stage in the cell cycle

of the irradiated cells and alterations in the vascular and connective tissue bed in which the neoplastically transformed cells reside. Conditioning factors which may also affect radiation carcinogenesis include species, strain, sex, age, and various proliferative stimuli and systemic factors. The distribution pattern of the radionuclides may influence the mechanism of carcinogenesis in the case of internal irradiation. The methods used and results obtained in the study of radiation carcinogenesis can also be applied to the study of the late effects of other environmental factors.

- 2560 DISTRIBUTION OF WR-2721 IN NORMAL AND MALIGNANT TISSUES OF MICE AND RATS BEARING SOLID TUMORS: DEPENDENCE ON TUMOR TYPE, DRUG DOSE AND SPECIES. (E.) Washburn, L. C. (Med. Div., Oak Ridge Assoc. Univs., Tenn.), J. E. Carlton, R. L. Hayes and J. M. Yuhas. *Radiat Res* 59(2):475-483, 1974.

S-2-(3-Aminopropylamino)ethylphosphorothioic acid (WR-2721) preferentially protects normal, as opposed to malignant, tissues of tumor-bearing mice from radiation injury. The major factor responsible for this difference in response appears to be the relatively poor absorption of the drug by the tumor. Normal and tumor tissue concentrations of ^{35}S -labeled WR-2721 were determined 30 minutes after injection of graded doses of the drug (1, 50, 100, or 300 mg/kg) into young male rats and mice bearing P-1798 lymphosarcomas, CA-755 adenocarcinomas (mice), RFT tumors, or Morris 7777 hepatomas (rats). Three of these solid tumors showed deficient drug absorption, although the Morris 7777 hepatoma absorbed WR-2721 as readily as the host's normal tissues. The relative concentration of the drug in normal and tumor tissues was independent of the injected dose between 50 and 300 mg/kg. The injection of tracer levels of WR-2721 (1 mg/kg) can be used to identify those tumors which exhibited deficient absorption, but not to quantitate the degree of deficiency. The relationship between the injected dose and tissue concentration, after correction for species differences in surface area, was species independent for the lungs, small intestine, and spleen, but species dependent for the kidney and liver. Thus, WR-2721 appears to be a promising agent for increasing the efficiency of solid tumor radiotherapy, providing that each tumor is considered individually.

- 2561 RELATIONSHIPS BETWEEN RADIATION DOSE AND SOMATIC RADIATION RISK. (Ger.) Jacobi, W. (Inst. Radiation Protection, Neuherberg, Germany). *Atomwirtschaft* 19(6):278-283, 1974.

Recent studies conducted in the USA and West Germany on relationships between radiation dose and somatic radiation risk are reviewed. A linear relationship was found between the radiation dose and the leukemia risk for the Hiroshima A-bomb survivors who had been exposed mainly to neutron radiation. Among the Nagasaki A-bomb survivors, who had been exposed mainly to γ -radiation, a nearly quadratic dose-risk relationship was established. In both cities, the

leukemia rate peaked between 1950 and 1955, after which it gradually decreased to the spontaneous leukemia level. The somatic cancer incidence significantly increased 15 to 20 yr after the A-bomb explosion. The carcinogenic effect of small doses of weakly ionizing γ -, β - and x-radiation was recently found to be substantially weaker than assumed earlier. In doses below 50 rad, the mean cancer risk that can be reasonably expected is probably not greater than 0.001% per rad. The Elkind effect occurred following exposure to γ - and x-radiation. Prolongation of the latency time with decreasing radiation doses was observed.

- 2562 INITIAL STUDIES WITH A LINE OF RADIORESISTANT RAT TUMOR CELLS. (E.) Nash, J. C. (U. Arkansas Med. Ctr., Little Rock), G. V. Dalrymple, A. J. Moss, Jr. and M. L. Baker. *Radiat Res* 60(2): 280-291, 1974.

- 2563 COSMIC RADIATION AT HIGH ALTITUDES AND U.S. CANCER MORTALITY, 1950-1969. (E.) Mason, T. J. (Natl. Cancer Inst., Bethesda, Md.) and R. W. Miller. *Radiat Res* 60(2):302-306, 1974.

- 2564 PULMONARY METASTASES FROM A THYROID CARCINOMA IN CHILDHOOD AFTER THORIUM-X TREATMENT. (Ger.) Knoop, U. (Munic. Hosp., Cologne, Germany) and O. Genz. *Z Kinderheilkd* 118(2):117-127, 1974.

See also:

- * (Rev): 2432, 2439
- * (Chem): 2514
- * (Viral): 2620

- 2565 DIFFERENCE IN DENSITY OF NUCLEAR PORES IN NORMAL AND MALIGNANT FIBROBLASTS OF SYRIAN HAMSTER. (E.) Rejthar, A. (Fac. Med., J.E. Purkyne U., Brno, Czechoslovakia) and J. Blumajer. *Neoplasma* 21(4):479-482, 1974.

The freeze-etching method was used to determine the number of pores/unit area of nuclear membrane in normal embryonal hamster fibroblasts (HEF) and B77 virus-transformed hamster fibroblasts (RBH). The structure and diameter of the pores were the same in HEF and RBH cells as revealed by electronmicroscopy. However, the HEF cells contained an average of 12.5 pores/ μm^2 , while the RBH cells had an average of 16.9 pores/ μm^2 : the difference is highly significant. The pores in the malignant RBH cells took up about 50% more of the nuclear envelope than the pores in the normal embryonal cells. The increase in pore density in the RBH cells may be due to an enhanced functional activity in RBH cells and/or to the oncogenic transformation.

- 2566 PROTEIN SYNTHESIZING ACTIVITIES OF RIBOSOME-LIKE STRUCTURES ISOLATED FROM AVIAN MYELOBLASTOSIS VIRUS IN CHICKEN CELL-FREE PROTEIN SYNTHESIS. (E.) Maly, A. (Lab. Biochem. Invest. Cancer, Czechoslovak Acad. Sci., Prague) and J. Rimán. *Neoplasma* 21(4):401-407, 1974.

The activity of isolated avian myeloblastosis virus (AMV)-occluded ribosome-like structures (VRs) in chicken cell-free protein synthesizing systems was compared with that of cytoplasmic ribosomes (CRs). Optimal conditions for the determination of poly(U)-directed polypheylalanine synthesis were tested with respect to the concentration of divalent (Mg^{2+}) and monovalent (K^+) ions, poly(U), and guanosine 5'-triphosphate. VRs mimicked the activity of CRs when added to the polypheylalanine synthesizing chicken cell-free system; however, the activity of the VRs was about 7 times lower than that of CRs. Addition of VRs to a chicken subcellular protein synthesizing system programmed by endogenous mRNA enhanced by about 50% the incorporation of amino acids into the protein.

- 2567 ISOLATION OF THE MAJOR VIRAL GLYCOPROTEIN AND A PUTATIVE PRECURSOR FROM CELLS TRANSFORMED BY AVIAN SARCOMA VIRUSES. (E.) Halpern, M. S. (Wistar Inst. Anat., Biol., Philadelphia, Pa.), D. P. Bolognesi and L. J. Lewandowski. *Proc Natl Acad Sci USA* 71(6):2342-2346, 1974.

Immune precipitation with a monospecific antiserum was used to study the synthesis of the major viral glycoprotein gp85. Labeled gp85 was detectable by the polyacrylamide gel electrophoresis of immune precipitates prepared from lysates of C/E chick embryo cells which had been transformed by clone-purified stocks of avian sarcoma virus B77 subgroup C (B77) or the Prague strain of Rous sarcoma virus subgroup C (PR RSV-C); the cells had been exposed to long-term labeling with radioactive amino acid or fucose. When immune precipitates were prepared from lysates of cells which had been pulse-labeled with radio-

active amino acids, the bulk of the precipitated counts appeared not in gp85, but in a heterogeneous protein fraction with a mean molecular wt of approximately 70,000; this fraction was designated p70. When, however, pulse labeling was followed by incubation of the cells in medium containing excess unlabeled amino acid, the bulk of the precipitated counts comigrated with gp85. Similar pulse-labeling experiments with radioactive fucose and glucosamine suggested that p70 represents an incompletely glycosylated precursor to gp85.

- 2568 VIROLOGICAL INVESTIGATIONS OF *HERPESVIRUS SAIMIRI*-INFECTED OWL MONKEYS. (E.) Neubauer, R. H. (Litton Bionetics, Inc., Kensington, Md.), W. C. Wallen, H. Rabin, G. R. Pearson and D. V. Ablashi. *J Med Primatol* 3(1):27-40, 1974.

Adult owl monkeys were inoculated i.m. and s.c. with a preparation of *Herpesvirus saimiri* (HVS), after which the HVS inocula, tissues from the infected animals, and cultured HVS-infected lymphoid cells were tested for the presence of type-C viruses. Examination of the infected monkeys failed to reveal the site of active viral replication. Virus was readily rescued from lymph node, lymphoma, heart, lung, liver, kidney, and skeletal muscle tissues cocultivated with vero cells, but neither infectious virus nor viral antigens were detected in these same tissues. Type-C RNA viruses were not detectable using RNA-dependent DNA polymerase or group-specific radioimmunoassay techniques. Similarly, nucleic acid base analogs failed to induce type-C viruses. These data lend further support to the view that HVS is the etiological agent responsible for HVS-induced lymphomas in owl monkeys.

- 2569 MINK CELL LINE MVLLU (CCL 64): FOCUS FORMATION AND THE GENERATION OF "NON-PRODUCER" TRANSFORMED CELL LINES WITH MURINE AND FELINE SARCOMA VIRUSES. (E.) Henderson, I. C. (Natl. Cancer Inst., Bethesda, Md.), M. M. Lieber and G. J. Todaro. *Virology* 60(1):282-287, 1974.

Cultures of fetal mink lung cells (CCL 64) were infected with the Kirsten strain of murine sarcoma-leukemia virus (KiMSV-MuLV). Within 5 days, distinct foci of morphologically transformed cells were seen; focus formation on the CCL 64 cells was about 100-fold less efficient than on the rat NRK cell line. Of 27 cultures of MSV-transformed mink cell foci, 20 were producing virus, while the other seven were polymerase-negative and appeared to be KiMSV nonproducer transformants. The Snyder-Theilen strain of feline sarcoma-leukemia virus (S-T FeSV-FeLV) also produced foci of transformed mink cells, while simian sarcoma-leukemia virus (SSV-SSAV) did not produce identifiable foci. The endogenous baboon type C virus, M7, simian sarcoma-associated virus (SSAV), gibbon sarcoma virus (GLV), feline leukemia virus (Rickard strain), RD-114 virus, the endogenous feline virus, CCC, AT-124 virus, and the S-tropic endogenous murine type virus also replicated well in CCL 64 cultures. MSV pseudotypes with various mammalian type C viruses were formed by in-

fecting one of the MSV-transformed mink cell cultures with various type C viruses; these pseudotypes of KiMSV all generated morphologically similar transformed foci when used to infect CCL 64 cells. Viral interference was studied by comparing the focus-forming ability of certain MSV pseudotypes on CCL 64 cells with their ability to form foci on mink cells infected 3 wk previously with the type C virus alone. Results suggested that the endogenous baboon virus group and the RD-114/CCC group of endogenous feline viruses are related.

- 2570 LACK OF SYNCYTIIUM FORMATION BY A TYPE C VIRUS-PRODUCING XC CELL LINE IN THE MIXED CULTURE CYTOPATHOGENICITY TEST. (E.) Chan, J. C. (M.D. Anderson Hosp., Tumor Inst., Houston, Tex.), N. Vera, J. L. East, S. Hiraki and L. Dmochowski. *Cancer Res* 34(3):468-473, 1974.

XC cells, derived from a Rous sarcoma virus-induced Wistar rat tumor, form syncytia when cultured in the presence of murine leukemia virus-producing mouse cells. However, one XC cell culture (designated as XC-v cells), found to produce type C virus particles, fails to form syncytia in the presence of murine leukemia virus-producing mouse cells. Coculture of XC-v cells and XC cells negative for type C virus particles leads to a moderate degree of syncytium formation. Infection of XC cells with either the Moloney (M) strain of mouse leukemia virus or type C virus particles released by XC-v cells results in the loss of ability of XC cells to form syncytia in the mixed culture cytopathogenicity test. The syncytium-forming ability of XC cells, therefore, is altered by the presence of a type C virus in these cells.

- 2571 COMPARISON OF SURFACE MATERIAL, CYTOPLASMIC FILAMENTS, AND INTERCELLULAR JUNCTIONS FROM UNTRANSFORMED AND TWO MOUSE SARCOMA VIRUS-TRANSFORMED CELL LINES. (E.) Dermer, G. B. (Hosp. Good Samaritan Med. Ctr., Los Angeles, Calif.), J. Lue and H. B. Neustein. *Cancer Res* 34(1):31-38, 1974.

Surface material, cytoplasmic filaments, and intercellular junctions of an untransformed normal rat kidney (NRK) cell line were compared with those of NRK cells transformed by a nonproductive B-7 mouse sarcoma virus and with NRK cells transformed by productive C-7 mouse sarcoma virus. Surface material was visualized by ruthenium red (RR) or by staining glycol methacrylate sections with acidic phosphotungstic acid. Glutaraldehyde-fixed normal and transformed cells were examined in subconfluent and confluent cultures by electron microscopy. B-7-transformed cells did not produce virus, whereas, C-7-transformed cells regularly exhibited budding. In subconfluent cultures where normal and transformed cells were dividing at equal rates, there was no difference in surface coats. With RR, there was a continuous, thin electron-dense layer at external surfaces of all cells while the staining of this layer by phosphotungstic acid was spotty. Differences in surface material were observed in confluent cultures, where untransformed cells were contact inhibited and did not increase in number while transformed cells continued

to divide. Both lines of transformed cells exhibited surface coats similar to those observed in subconfluent cultures, even where cells were closely apposed, while the NRK cells exhibited considerably more extracellular RR-positive material, particularly at regions of cell contact. This material appeared to be involved in cell adhesion. Also in confluent cultures, the peripheral cytoplasm of NRK cells had many 80 Å diameter filaments which were aggregated into bundles and were most abundant near regions of cell-to-cell apposition. The filaments attached to material beneath plasma membranes at sites of intercellular junctions. Transformed cells were clearly deficient in cytoplasmic filaments and intercellular junctions. In this system, RR-positive material at cell surfaces and the presence of intercellular junctions with associated cytoplasmic filaments may have a role in the regulation of cell growth and multiplication.

- 2572 THE SPECIFICITY OF DIMETHYLBENZYLRIFAMPICIN AS AN INHIBITOR OF VIRAL INDUCED TRANSFORMATION. (E.) Smith, H. S. (Sch. Public Health, U. California, Berkeley) and A. J. Hackett. *Proc Natl Acad Sci USA* 71(7):2770-2772, 1974.

A variant BALB/3T3 cell line that is resistant to 10 µg/ml dimethylbenzylrifampicin (DMB) was used to study the effects of DMB on transformation by murine sarcoma virus (MSV), an RNA-containing oncornavirus, and on transformation by simian virus 40 (SV40), a DNA-containing virus that lacks reverse transcriptase activity. MSV transformation of resistant BALB/3T3 cells was inhibited more than 150-fold in the presence of 10 µg/ml DMB plus 1 µg/ml amphotericin B. No foci were present at a virus concentration that produced 162 foci in the absence of drugs. Under the same conditions, SV40 transformation was essentially unaffected. SV40-induced transformation frequency was 3% in the presence of both drugs compared with 4% in their absence. The resistant variants are not dependent on DMB for growth and are probably not blocked at the level of drug uptake. The data show that DMB specifically inhibits oncornavirus-induced transformation rather than nonspecifically inhibiting cellular growth or transformation.

- 2573 EXPERIMENTAL SIMIAN VIRUS 40 INFECTION OF NORMAL AND IMMUNOSUPPRESSED SPIDER MONKEYS. (E.) Cole, G. A. (Sch. Hygiene Public Health, Johns Hopkins U., Baltimore, Md.) and K. V. Shah. *Acta Virol (Praha)* 18(1):65-69, 1974.

Ten female spider monkeys were each inoculated both s.c. and i.v. with simian virus 40 (SV40; 3×10^8 median tissue culture infective dose). Six of these animals were immunosuppressed with cyclophosphamide given s.c. one day (100 mg/kg) and eight days (50 mg/kg) after virus inoculation. The course of SV40 infection in the 4 normal and the 6 immunosuppressed animals was assessed by monitoring each animal for the appearance of viremia, viruria, and virus-specific antibodies. Viremia was present in two monkeys from each group only on the second day after in-

fection. None of the animals in either group showed detectable virus in the urine. Although the levels of neutralizing antibodies at 2 wk postinfection did not significantly differ between the normal and cyclophosphamide-treated monkeys, the treated animals all eventually displayed peak titers which were approximately 10-fold greater than those of the control group. These elevated antibody levels may have been due to an enhanced immunogenic stimulus resulting from the potentiation of virus replication during the period of cyclophosphamide administration. Limited attempts to demonstrate persistence of the virus in the infected animals were unsuccessful. None of the experimental animals developed tumors.

- 2574 PHYSICAL AND CHEMICAL PROPERTIES OF AN ONCORNAVIRUS ASSOCIATED WITH A MURINE ADRENAL CARCINOMA CELL LINE. (E.) Burnette, W. N. (Vanderbilt U. Sch. Med., Nashville, Tenn.), C. H. Riggan and W. M. Mitchell. *J Virol* 14(1):110-115, 1974.

A type-C oncornavirus was isolated from a continuous line of murine adrenal carcinoma cells (clone Y-1, ATCC no. CCL-79) maintained in culture. The particles had a buoyant density of 1.165 g/cm³, exhibited typical type-C morphology under the electron microscope, possessed an RNA-dependent DNA polymerase, and had a high-molecular wt RNA (6.1×10^6) which could be denatured to a homogeneous lower molecular wt species (3.2×10^6) when extracted from rapidly harvested "immature" virions. The virus is antigenically related to the N-tropic viruses of BALB/c, C58, and AKR mouse cells and the Moloney leukemia virus. In addition, the Y-1 virus exhibited a number of polypeptides which comigrated with those of AKR and Moloney viruses, including what has been termed the p30 or 30,000 molecular wt group-specific protein - the major internal protein constituent and antigenic determinant of the type-C viruses. The electrophoretic pattern of these virus proteins was dissimilar to those for both the type-C avian myeloblastosis virus and the type-B murine mammary tumor virus.

- 2575 PREVENTION OF FRIEND VIRUS LEUKEMOGENESIS BY CONCAVALIN A. I. DETECTION OF DORMANT VIRUS AND ROLE OF HUMORAL ANTIBODY IN PROTECTED MICE. (E.) Kateley, J. R. (Albert Einstein Med. Ctr., Philadelphia, Pa.) and H. Friedman. *J Natl Cancer Inst* 53(1):151-158, 1974.

Friend leukemia virus (FLV, 0.2 ml) leukemogenesis was prevented when FLV was treated with Concanavalin A (Con A, 250 µg) before i.p. injection into BALB/c mice. Such protection was not mediated by neutralizing or cytotoxic antibody, although 60% of mice infected with Con A-treated FLV were protected from reinfection with a lethal dose of FLV. Spleen size of mice infected with Con A-treated FLV was normal up to 50 days after challenge, but the humoral immune response to sheep RBC was partially suppressed. Tissue culture, as well as cell and serum transfer experiments, demonstrated that infectious virus was present in protected mice. Since Con A agglutinates oncornaviruses such as FLV, this presumably accounts for a reduced infectivity *in vivo*; however, mechanisms

other than humoral immunity that might account for the protection from the overt symptoms of leukemogenesis include: stimulation of cell-mediated immunity, activation of macrophages, stimulation of antibody cytophilic for macrophages, and nonimmunologic mechanisms.

- 2576 ISOLATION AND CHARACTERIZATION OF RNA-DIRECTED DNA POLYMERASE FROM A B-TYPE RNA TUMOR VIRUS. (E.) Dion, A. S. (Inst. Med. Res., Camden, N.J.), A. B. Vaidya, G. S. Fout and D. H. Moore. *J Virol* 14(1):40-46, 1974.

RNA-directed DNA polymerase was isolated from milk-borne B-type murine mammary tumor virus (MuMTV) of the RIII mouse strain. The DNA polymerase sedimented as a single component with an estimated $S_{20,w}$ of 5.5S to 5.7S; the molecular wt was estimated at 98,000-102,000. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the phosphocellulose peak enzyme fraction demonstrated the enrichment of only one protein, which possessed a molecular wt of 100,000 and was presumably the polymerase enzyme. The purified enzyme was completely template dependent, responding most efficiently to poly(rC)·oligo(dG); relatively less response was observed with "activated" salmon sperm DNA and MuMTV 70S RNA. Stability studies indicated differential lability dependent on the exogenous template used to monitor activity. The results did not support the existence of two viral DNA polymerases in RIII milk.

- 2577 NUCLEOTIDE SEQUENCE RELATIONSHIPS OF AVIAN RNA TUMOR VIRUSES: MEASUREMENT OF THE DELETION IN A TRANSFORMATION-DEFECTIVE MUTANT OF ROUS SARCOMA VIRUS. (E.) Neiman, P. E. (U. Washington Sch. Med., Seattle), S. E. Wright, C. McMillin and D. MacDonnell. *J Virol* 13(4):837-846, 1974.

Stocks of cloned helper-independent Rous sarcoma virus (RSV) spontaneously segregate transformation-defective (td) mutants that appear to have an RNA genome composed of smaller subunits than those of the parent virus. Differential hybridization and competitive hybridization techniques involving reactions between viral RNA and proviral sequences in host cell DNA (under conditions of initial DNA excess) were used to measure the extent of the deletion in a td mutant of the Prague strain (Pr) of RSV (RrRSV-C). Viral 60-70S RNA sequences labeled to 1 to 5×10^7 cpm/µg with ¹²⁵I were characterized with respect to their properties in hybridization reactions and were used to reinforce data obtained with ³H-RNA of lower specific activity. About $13 \pm 3\%$ of the PrRSV-C sequences forming hybrids with DNA from virus-induced sarcomas appeared to be deleted from the genome of td PrRSV-C. Studies comparing the hybridization of RNA from PrRSV-C and td PrRSV-C with RSV-related sequences in normal cells, and competition experiments with RNA from the endogenous chicken oncornavirus Rous-associated virus type O (RAV-O) showed most, if not all, of the RNA sequences of PrRSV-C deleted from its transformation-defective mutant are not represented in normal chicken DNA. Competition studies with a leukosis virus, RAV-7, indicated

that this virus also lacks a genome segment of about the same size as the deletion in the td mutant. Finally, the genome of all three "exogenous" viruses lacked a small segment (about 12%) of sequences present in the endogenous provirus of RAV-O.

- 2578 RNA-DEPENDENT DNA POLYMERASE (REVERSE TRANSCRIPTASE) FROM AVIAN MYELOBLASTOSIS VIRUS: A ZINC METALLOENZYME. (E.) Auld, D. S. (Peter Bent Brigham Hosp., Boston, Mass.), H. Kawaguchi, D. M. Livingston and B. L. Vallee. *Proc Natl Acad Sci USA* 71(5):2091-2095, 1974.

Differences in the metabolism of zinc by normal and leukemic leucocytes led to the hypothesis that a zinc-dependent enzyme system is critical in the pathophysiology of myelogenous and lymphatic leukemia. To investigate the relationship between zinc and the initiation of leukemia in chickens by the avian myeloblastosis virus (AMV), the metalloenzyme nature of its reverse transcriptase was studied. The data indicated that this protein is a zinc metalloenzyme, thereby confirming the postulated relationship between zinc and the leukemic process. A novel system for metal analysis incorporating microwave-induced emission spectrometry combined with gel exclusion chromatography was designed. The method provides precision and reproducibility, and can be used with μ l samples containing 10^{-12} to 10^{-14} g-atoms of metal. The chromatographic fraction of AMV polymerase with the highest enzymatic activity contains 1.8×10^{-11} g-atoms of zinc/1.6 μ g of protein, corresponding to either 1.8 or 2.0 g-atoms of zinc/mole of enzyme for a molecular wt of 1.6 or 1.8×10^5 . Copper, iron, and manganese were not present in detectable quantities. Agents known to chelate zinc inhibited the activity of the enzyme, while their nonchelating isomers did not.

- 2579 COMPARATIVE INHIBITION OF PURIFIED DNA POLYMERASES FROM MURINE LEUKEMIA VIRUS AND HUMAN LYMPHOCYTES BY 1- β -D-ARABINOFURANOSYLCYTOSINE 5'-TRIPHOSPHATE. (E.) Schrecker, A. W. (Natl. Cancer Inst., Bethesda, Md.), R. G. Smith and R. G. Gallo. *Cancer Res* 34(2):286-292, 1974.

The K_m for cytidine-5'-triphosphate and the K_i for 1- β -D-arabinofuranosylcytosine 5'-triphosphate (ara-CTP) were determined with DNA polymerases purified by diethylaminoethyl cellulose and phosphocellulose chromatography from Rauscher murine leukemia virus, from human blood lymphocytes, and from a human lymphoblastoid cell line. Inhibition of the viral reverse transcriptase varied with the template/primer used. With poly(rI)·oligo(dC) (rI_n·dC₁₂₋₁₈) as the synthetic template/primer, this enzyme had a greater relative affinity for the inhibitor than had the cellular enzymes in the presence of DNA. However, when DNA was the template, inhibition of the viral enzyme was decreased considerably. DNA polymerase I of normal human lymphoid cells, which was separated from the lower-molecular-weight polymerase II and could be assayed only in the presence of DNA, had a lower relative affinity for ara-CTP than the viral reverse transcriptase directed by poly(rI)·oligo(dC). How-

ever, in the presence of magnesium ions and a DNA template, the viral enzyme was inhibited far less than either of the cellular enzymes. Since ara-CTP inhibits both viral and cellular DNA polymerases and inhibition varies with the template used, the compound cannot be considered a specific inhibitor of reverse transcriptase in studies of virus-cell interactions. The suggestion that polymerase I is involved in DNA replication is consistent with the finding that, in the presence of "activated" DNA, it is inhibited to a greater extent by ara-CTP than is polymerase II.

- 2580 ISOLATION AND PARTIAL CHARACTERIZATION OF DIFFERENT DEFECTIVE DNA MOLECULES DERIVED FROM POLYOMA VIRUS. (E.) Fried, M. (Imperial Cancer Res. Fund, London, England). *J Virol* 13(5):939-946, 1974.

Supercoiled DNA molecules purified from mouse cells infected with high-multiplicity-passaged polyoma virus have a broader size distribution and sediment more slowly than DNA derived from low-multiplicity-passaged virus. The shorter molecules are predominantly noninfectious. Virus populations containing distinct size classes of defective virus DNA were isolated by growing virus from single cells infected by a defective and nondefective helper virus (infectious center). This technique probably results in the cloning of defective virus particles. By applying the infectious center method to DNA from various fractions of sucrose gradients, it was possible to obtain shorter circular DNA molecules ranging in size from 50-95% of the unit-length polyoma DNA molecule. The shorter molecules in any one preparation were homogeneous in size. This class size was retained upon repeated passage of crude viral lysates at high multiplicity. Thus far, all the purified shorter DNA molecules tested have appeared to be noninfectious and largely resistant to cleavage by the R₁ restriction enzyme. Some of the purified defective molecules interfered with the production of infectious virus upon coinfection with unit-length infectious polyoma DNA.

- 2581 PREVENTION OF 334C MURINE VIRUS-INDUCED LEUKEMIA BY TRANSMISSION OF MATERNAL IMMUNITY TO OFFSPRING. (E.) Buffett, R. F. (Roswell Park Mem. Inst., New York, N.Y.). *Cancer Res* 34(3):559-563, 1974.

Random-bred Ha/ICR Swiss mice were protected against development of virus-induced leukemia late in life when they were suckled on female mice immunized as adults with 334C murine leukemia virus, a member of the Friend-Moloney-Rauscher subgroup of murine leukemia viruses. Young adult female mice were immunized with one to three injections of virus filtrate from organs of leukemic mice at weekly intervals and were mated during or after immunization. Offspring were challenged at birth by injection with 334C virus and then suckled on immunized females until weaned. The incidence of leukemia was reduced to an average of 10% in offspring from immunized females, compared with an average of 72% in offspring from nonimmunized

females. The capability of virus-immunized females to protect their young extended over a period of 5 to 6 months. Neonatal mice also were protected against development of leukemia when they were suckled on virus-immunized females either before or after infection by vertically transmitted 334C virus in reciprocal foster nursing experiments. Offspring were suckled on virus-immunized mothers for 2, 8, and 14 days before being transferred to virus-infected females. Leukemia developed in 36, 15, and 14% of offspring, as compared with 71, 38, and 7% in control litters (offspring from nonimmunized mothers suckled on virus-infected females). When offspring were suckled on virus-infected mothers for 2, 8, and 14 days before being transferred for suckling to virus-immunized females, leukemia developed in 6, 33, and 81% as compared with 83, 68, and 72% in control litters (virus-infected offspring suckled on normal females).

- 2582 LOW RESISTANCE JUNCTIONS BETWEEN NORMAL AND BETWEEN VIRUS TRANSFORMED FIBROBLASTS IN TISSUE CULTURE. (E.) O'Laigue, P. (Harvard Med. Sch., Boston, Mass.) and H. Dalen. *Exp Cell Res* 86(2):374-382, 1974.

The occurrence of low-resistance junctions between normal chick embryo fibroblasts and between fibroblasts transformed with Rous sarcoma virus in tissue culture was studied with intracellular microelectrodes. These junctions were present between normal chick fibroblasts in proliferating cultures as well as between cells in "density-dependent inhibited cultures." Mechanical injury to a fibroblast within a small group of coupled cells caused the injured cell to uncouple immediately from its neighbors without interrupting the coupling between the uninjured cells. In the case of fibroblasts transformed by a Rous sarcoma virus, the low-resistance junctions were present when the cells first appeared transformed and remained thereafter. The data indicate that low-resistance junctions between contacted fibroblasts in culture may exist throughout the contact period; thus fibroblasts in a state of contact inhibition of movement are probably electrically coupled. These low-resistance contacts between cells may prove important in coordinating cellular activity.

- 2583 ANIMAL VIRUS USED ON CANCER PATIENTS. (E.) Anonymous. *Sci News* 106(10):149-150, 1974.

Twenty patients with advanced cancers were immunized with a killed Rauscher leukemia virus every 2 wk for 8 wk. Two-thirds of these patients developed cellular immunity against the virus; the responses did not differ significantly among patients with different types of cancer or receiving different types of therapy. Half of the patients also developed antibodies against the virus. These responses were greatest in patients with melanoma and in patients receiving chemotherapy plus bacillus Calmette Guérin (BCG). The responses were least pronounced in patients with acute leukemia and solid tumors other than melanoma and in those receiving drugs without BCG. Some of the patients are still experiencing remissions, probably

due to chemotherapy and BCG. Immunization with the cancer virus produced no undesirable side effects. Other studies have shown that BCG added to chemotherapy clearly prolongs cancer remission and patient survival. These results indicate a promising future for immunotherapy in cancer patients.

- 2584 EPITHELIAL CELL CULTURES FROM NORMAL GLANDULAR TISSUE OF MICE. (E.) Owens, R. B. (Sch. Public Health, U. California, Berkeley), H. S. Smith and A. J. Hackett. *J Natl Cancer Inst* 53(1):261-269, 1974.

The growth properties, tumorigenicity, virus production, and maintenance of differentiated functions of nine epithelial cell strains established from normal mouse liver, mammary gland, ovary and ear skin are described. These strains continue to show morphologic and ultrastructural features typical of epithelial cells after 10-50 subcultures. In addition several strains continue to form secretory vesicles, on confluent cell sheets. Although all these strains were derived from normal tissues, none has remained completely normal in cultures. All strains display bimodal distributions of chromosomes numbers. Although most cells in each strain contain the diploid number, each line includes a minority population of cells with near triploid or tetraploid numbers of chromosomes. Five strains produced tumors (benign cystadenomas, adenocarcinomas, and sarcomas) when inoculated into isogenic mice. Type-C oncornaviruses were seen in all but two strains.

- 2585 TUMOR INDUCTION BY MURINE SARCOMA VIRUS IN AKR AND C58 MICE: REDUCTION OF TUMOR REGRESSION ASSOCIATED WITH APPEARANCE OF GROSS LEUKEMIA VIRUS PSEUDOTYPES. (E.) Chieco-Bianchi, L. (Inst. Pathol. Anat., U. Padua, Italy), A. Colombatti, D. Collavo, F. Sento, T. Aoki and P. J. Fischinger. *J Exp Med* 140(5):1162-1179, 1974.

Adult AKR and C58 mice injected i.m. with murine sarcoma virus, Moloney isolate (M-MSV), developed a high incidence of nonregressing local tumors. Histologically, these tumors revealed the typical pleomorphism of M-MSV sarcomas; in some cases, however, the neoplastic tissue showed a nodular or diffuse growth of monomorphic myoblastlike cells reminiscent of clonal aggregates. No depression of immune reactivity was found in the M-MSV-treated mice as evaluated by direct hemolytic plaque-forming cells against sheep RBC and by virus-neutralizing antibody production. Neutralization assay showed that the MSV recovered from the induced tumors was a Gross (G)-MSV pseudotype. Moreover, the tumor cell suspensions absorbed out cytotoxic antibody directed against G-cell surface antigens. Thus it appeared that MSV with the envelope characteristics of endogenous G leukemia virus had formed *in vivo* via a phenotypic mixing phenomenon. The failure of the tumors to regress is attributed primarily to the partial unresponsiveness of the host immune reactivity toward G-murine leukemia virus (MuLV)-specified antigens. Since the MSV tumors arose in AKR mice after a very long latent period, it was possible that the relative resistance shown

by these animals was dependent on immunologic mechanisms. In fact, M-MSV-treated AKR mice immunodepressed by goat antimouse lymphocyte serum or rendered partially tolerant by neonatal M-MuLV inoculation developed a higher incidence of sarcomas with a shorter latency. The MSV recovered from these early tumors proved to be the original Moloney pseudotype. Thus, AKR and C58 type C endogenous viruses can compete successfully with exogenous M-MuLV as helpers for *in vivo* MSV replication.

2586 ANALYSIS OF MINIMAL FUNCTIONS OF SIMIAN VIRUS 40. IV. ONCOGENIC TRANSFORMATION OF SYRIAN HAMSTER KIDNEY CELLS *IN VITRO* BY BETA-PROPIOLACTONE INACTIVATED SV40. (E.) Seemayer, N. H. (Wistar Inst. Anat., Biol., Philadelphia, Pa.) and V. Defendi. *Arch Gesamte Virusforsch* 45(4):301-308, 1974.

CV-1 and primary Syrian hamster kidney cell cultures were infected with progressively beta-propiolactone (BPL)-inactivated simian virus 40 (SV40). The kinetics of inactivation of different functions of SV40 after treatment with BPL were analyzed. The most sensitive function was infectivity which, after a reduction of approximately 4 log₁₀ step, showed a pronounced "tailing effect." Induction of T-antigen and DNA-synthesis showed a similar tailing effect, but these two functions were more resistant to BPL inactivation than was infectivity. Syrian hamster kidney cells transformed *in vitro* by BPL-inactivated SV40 showed the same morphology as cells transformed by noninactivated SV40. Virtually all such cells contained specific T-antigen and produced tumors after s.c. inoculation into Syrian hamsters. Infectious SV40 could not be detected in concentrated extracts of transformed cells. The discrepancy between the loss of infectivity and the high residual transforming capability of BPL-treated SV40 contraindicates the use of BPL for the inactivation of potentially oncogenic viruses.

2587 HAEMOGLOBIN SYNTHESIS IN INDUCIBLE, UN-INDUCIBLE AND HYBRID FRIEND CELL CLONES. (E.) Paul, J. (Beatson Inst. Cancer Res., Glasgow, Scotland) and I. Hickey. *Exp Cell Res* 87(1):20-30, 1974.

Less than 1% of the cells of clone 707 of the Friend virus-induced erythroleukemic cell line stained detectably for hemoglobin with benzidine. On treatment with 2% dimethylsulphoxide (DMSO), the fraction of staining cells increased to 70-80%. Line Fw, which has a similar origin as clone 707, did not respond to DMSO, although up to 7-8% of these cells stained for hemoglobin when grown in intraperitoneal perfusion chambers. Clone 707 did not appear to contain subpopulations of noninducible cells, nor did the Fw line appear to contain a subpopulation of inducible cells. A 5-bromodeoxyuridine (BUDR)-resistant derivative of clone 707 (clone 707B2/7) was isolated and shown to be incapable of incorporating ³H-thymidine. A thioguanine-resistant derivative of line Fw (clone FwT6/4) was incapable of incorporating ³H-hypoxanthine. Hybrids were prepared by fusion

cells of clone 707B2/7 and clone FwT6/4 in the presence of inactivated Sendai virus and selecting the hybrids in HAT medium. The hybrids contained chromosomes from both parents and could be induced by DMSO treatment to form an increased fraction of hemoglobinized cells.

2588 70S-RNA-CONTAINING PARTICLES IN HUMAN LEUKEMIAS. (Ger.) Hehlmann, R. (Inst. Cancer Res., Columbia U., New York, N.Y.), D. Kufe, W. Baxt and S. Spiegelman. *Verhandl Dtsch Ges Inn Med* 79:402-405, 1973.

Particles containing 70s-RNA were detected in human leukemias, and characteristic properties of RNA tumor viruses in human leukemic cells were identified by molecular hybridization of nucleic acids and by the simultaneous detection of different biochemical and physical characteristics of carcinogenic RNA viruses in human neoplasms. Pronounced homology was demonstrated between leukemia viruses in mice and rats by the hybridization and comparison of tritiated DNA synthesized from mouse leukemia virus RNA and leukocyte RNA from leukemic rats. Similar experiments with RNA isolated from the cytoplasm of human leukemic cells revealed homology of RNA from human lymphatic, myeloid, acute, and chronic leukemias with mouse leukemia virus RNA. High molecular weight of RNA of the 70s type, the presence of reverse transcriptase, a base frequency homologous with that of mouse leukemia virus, and a density typical of the 70s-RNA-DNA polymerase complex are the basic features characteristic of RNA tumor viruses. The findings supply evidence on the participation of virus in human malignancy.

2589 THE CYTOLOGY AND CYTOCHEMISTRY OF LEUKEMIA CELLS INDUCED BY FRIEND'S VIRUS DURING DIFFERENTIATION IN COMPARISON WITH HUMAN LEUKEMIA CELLS. (Ger.) Knebel, A. (Pediatr. Clin., U. Hamburg, Germany), H. Beckmann and N. Kluge. *Verhandl Dtsch Ges Inn Med* 79:377-378, 1973.

Comparative cytological and cytochemical investigations of Friend's virus leukemia cells during dimethylsulfoxide-induced differentiation and of human leukemia cells with characteristics of erythropoietic differentiation are described. The paranuclear positive acid phosphatase activity, typical of human leukemia cells, is weak in Friend's virus leukemia cells and is due to species-specific differences. Non-hemoglobin iron is detectable in Friend's virus leukemia cells by the silver sulfide reaction. This non-hemoglobin iron shows the same cytochemical behavior as in human leukemia cells. Unlike the negative to weak alpha-N-esterase activity of human leukemic blasts with erythropoietic differentiation characteristics, the alpha-N-esterase activity of Friend's virus leukemia cells and of human erythropoietic cells found in pernicious anemia and in Giuglielmo's disease is strongly positive. This may indicate an advanced differentiation of the cell population in Friend's virus leukemia towards erythropoiesis, since mature human leukemic blasts are also positive. Among the

different cytochemical tests carried out, Lepehne's reaction was found to be the only one to show changes during the induced differentiation of Friend's virus leukemia cells.

- 2590 PRESENCE OF H RNase ACTIVITY NOT ASSOCIATED WITH THE REVERSE TRANSCRIPTASE ACTIVITY IN VIRIONS OF MOLONEY MURINE SARCOMA. (Fr.) Olofsson, B. (Lab. Hematol. Experiment., Hosp. Saint-Louis, Paris, France), R. Hamelin, P. Tchen, and A. Tavitian. *C R Acad Sc Ser D (Paris)* Vol. 278:2851-2854, 1974.

The nature of H RNase activity in Moloney murine sarcoma virus (MSV-M) produced by transformed rat fibroblast cell line 78 A1 was studied and compared with that found in avian myeloblastosis virus. The virus suspensions were activated with non-ionic NP 40 detergent. The H RNase found in MSV-M is nearly comparable with that present in avian myeloblastosis virus, but, unlike that found in the latter, is not associated with purified reverse transcriptase. The MSV-M virions synthesize an essentially monocatenary DNA in endogenous reaction *in vitro*. The transcription of murine viral RNA into DNA in the viral replication cycle in the host cells may necessitate a H RNase that may be either a cellular enzyme, or a viral enzyme incorporated in the virions. Further studies are necessary to determine the cellular or viral origin and the localization of this H RNase activity in the virions.

- 2591 ISOLATION AND CHARACTERIZATION OF "8S" RNA IN MURINE SARCOMA VIRUS-INFECTED CELLS. (E.) Robert-Robin, J. (St. Louis Hosp., Paris, France), R. Emanoil-Ravicovitch, M. Brazillier and M. Boiron. *Biochem Biophys Res Commun* 60(3):965-975, 1974.

Three new 8S RNA species were identified in rat cells chronically infected with Moloney murine sarcoma virus. Two have identical electrophoretic mobilities, nucleotide compositions, and fingerprints with the 8S_A and 8S_B RNAs recently found in the mouse sarcoma-leukemia virus, M-MSV (MLV); the third cellular 8S component, called X, is not incorporated in the virus. Experiments of cellular 8S RNA heat treatment suggest that the 8S_A and 8S_B RNAs are conformational isomers of each other. The different relative proportions of the two A and B components in the host cell and in the virus are discussed. No role or specific function of this new 8S RNA is yet known. The presence of a similar RNA in noninfected rat cells appears to indicate that it is a usual cellular RNA incorporated in the virus upon budding.

- 2592 SEROLOGICAL ANALYSIS OF REVERSE TRANSCRIPTASE OF THE MASON-PFIZER MONKEY VIRUS. (E.) Yaniv, A. (Columbia U. Coll. Physicians Surgeons, New York, N.Y.), T. Ohno, D. Kacian, D. Colcher, S. Witkin, J. Schlom and S. Spiegelman. *Virology* 59(1):335-338, 1974.

Antiserum prepared against the partially purified DNA polymerase of Mason-Pfizer monkey virus (MPMV)

neutralized the endogenous DNA polymerase of that virus and of X381 virus, an agent which is morphologically indistinguishable from MPMV and which was isolated from cultures prepared from the lactating mammary gland of a rhesus monkey. Anti-MPMV DNA polymerase did not inhibit the DNA polymerase activity of avian myeloblastosis virus, Rauscher and Friend murine leukemia viruses, feline leukemia virus, murine mammary tumor virus, or simian sarcoma virus.

- 2593 SEROLOGICAL CLASSIFICATION OF TWO MOUSE ADENOVIRUSES. BRIEF REPORT. (E.) van der Veen, J. (St. Elizabeth Hosp., Tilburg, Netherlands) and A. Mes. *Arch Gesamte Virusforsch* 45(4):386-387, 1974.

Antisera to mouse adenovirus strains FL and K87 were prepared in mice and guinea pigs. Cross-neutralization and complement fixation (CF) tests were then performed using primary suckling mouse kidney cell cultures. Sera from control mice and preimmunization sera from guinea pigs were negative for neutralizing and CF antibodies to strains FL and K87. No cross-reactions were found in the neutralization and CF tests between the two virus strains. In addition, the antisera to the mouse adenoviruses failed to react with CF antigen to human adenovirus type 2, although cross-reactions between human and mouse adenoviruses could be demonstrated by CF tests with human sera. All of six sera from convalescent patients infected with adenovirus reacted in CF tests with the two mouse adenoviruses as well as with human adenovirus type 2. Six human sera without detectable CF antibody to human adenovirus were also negative for CF antibody to the mouse adenoviruses. The titers of the convalescent sera to human adenovirus were 2-16 times higher than those to the mouse adenoviruses. Thus the mouse adenovirus strains FL and K87 are distinct serotypes and should be designated mouse adenovirus types 1 and 2.

- 2594 ACCELERATED CLEARANCE OF EXOGENOUSLY ADMINISTERED ERYTHROPOIETIN BY MICE WITH RAUSCHER VIRAL LEUKEMIA. (E.) Okunewick, J. P. (Allegheny Gen. Hosp., Pittsburgh, Pa.) and P. Erhard. *Cancer Res* 34(5):917-919, 1974.

Both the endogenous plasma erythropoietin levels and the rate of plasma clearance of injected erythropoietin were investigated in SJL/J mice that had been rendered leukemic by the injection of Rauscher virus. The results show an elevated level of endogenous erythropoietin coupled with an accelerated rate of erythropoietin clearance. These results are inconsistent with the hypothesis previously suggested that erythropoietin production is impaired by Rauscher leukemia. As an alternative, it is proposed that as a result of the leukemia both erythropoietin production and clearance are accelerated to such a degree that very little reserve production capacity remains to allow for additional hormone synthesis in response to the stimuli of extreme anemia or bleeding.

- 2595 LEUKAEMOGENIC EFFECT OF REPEATED INOCULATIONS WITH SMALL DOSES OF TENNANT VIRUS IN BALB/c MICE. (E.) Bentvelzen, P. (Radiobiol. Inst. TNO, Rijswijk, Netherlands) and J. Brinkhof. *Nature* 251(5471):155-156, 1974.

A 10% cell-free extract was prepared with B/Tennant leukemia virus isolated from a spontaneous lymphosarcoma of BALB/c mice. Six-wk-old BALB/c females were injected i.p. thrice weekly with 10 ml aliquots of this preparation. Virus dilutions up to 1000-fold were still fully leukemogenic, with higher virus doses or repeated inoculations tending to shorten the latency period. There was no indication that dose fractionation led to a lower incidence of longer latency. In fact, repeated inoculations with low virus doses produced a significantly higher incidence of leukemia than a single injection with a much higher dose. Continuous exposure to even very small numbers of virus particles may induce immunological unresponsiveness to the virus, or, alternatively, autointerference induced by a moderate dose of virus may play an important role in the propagation in the host of small number of particles.

- 2596 STEM CELL GROWTH AND PRODUCTION OF COLONY-STIMULATING FACTOR IN RAUSCHER VIRUS-INFECTED CBA/J MICE. (E.) Iturriza, R. G. (Dept. Clin. Physiol., U. Ulm, Germany) and H. J. Seidel. *J Natl Cancer Inst* 53(2):487-492, 1974.

Female CBA/J mice were injected i.p. with a Rauscher leukemia virus preparation. The compartment sizes of pluripotent stem cells (CFU_s) and *in vitro* colony-forming cells (CFU_c) from these mice decreased 2 days after virus infection. This decrease was most pronounced in the CFU_c in the spleen, which contained about 10% of the normal levels. Two to six wk after infection, however, the CFU_s and CFU_c compartment sizes in the spleen rapidly increased to up to 30 times the normal values. In the serum, spontaneous colony-stimulating activity (CSA) was not detectably elevated. In contrast, the CSA was high in the spleen preparations 2 and 14 days after infection. Five g of endotoxin was injected into infected mice. After 5 or more days, the concentration of the colony-stimulating factor in the spleen began to fall, reaching zero by day 42. Due to the increase in organ size 21 days after infection, the total CSA in the spleen was about 5 times the normal concentration.

- 2597 ISOLATION OF A TRANSPLANTABLE CELL LINE INDUCED BY THE MC29 AVIAN LEUKOSIS VIRUS. (E.) Langlois, A. J. (Duke U. Med. Ctr., Durham, N. C.), K. Lapis, R. Ishizaki, J. W. Beard and D. P. Bolognesi. *Cancer Res* 34(6):1457-1464, 1974.

A transplantable cell line was isolated from a liver tumor induced by the MC29 strain of avian leukosis virus. It was found that its ability to develop into a tumor when inoculated in recipient birds (both i.m. and in the wing web) was dependent on a morphological alteration which took place after

the cells had been in culture for some time. The transplantable cell exhibited unusual properties, compared with other MC29 altered cells, and appears to represent a unique target cell for the MC29 virus. Tumors appeared at the site of inoculation at about 10 days after administration of MC29 tumor cells and were well-developed by 21 days postinoculation. The occasional tumors induced with MC29 virus or MC29-altered chicken embryo fibroblasts (CEC) required 40-60 days to appear. Tumors induced with the virus or MC29-altered CEC were morphologically distinct from those induced by material from tumor cell cultures; when placed in culture, tumor cells showed the morphology and growth characteristics of those inoculated. Antigen analysis indicated that MC29 CEC retained 65% of avian virus group-specific antigens and the virus about 35%, whereas cells from a 90-day culture retained only 4% of the antigen. The detectable antigen was virus associated since it was sedimentable and was measurable only after disruption of particles with ether.

- 2598 DEVELOPMENT OF LEUKEMIA IN RATS WITH TUMORS INDUCED BY CHICKEN SARCOMA VIRUS. (E.) Svec, F. (Cancer Res. Inst., Bratislava, Czechoslovakia), E. Hlavay, P. Kossey, J. Matoska and M. Hladka. *J Natl Cancer Inst* 52(1):31-36, 1974.

RBA myeloid leukemia developed in Sprague-Dawley rats inoculated with chicken sarcoma virus. At the site of inoculation, RBA rat sarcoma (RBA-Sa) tumors appeared, which contained foci of leukemic cells in addition to sarcomatous tissue. RBA-Sa, when transplanted s.c. gave rise, at the site of inoculation, to sarcomas containing disseminated leukemic cells and generalized leukemia (RBA-Le). RBA leukemic liver and spleen cells, transplanted i.p. into rats of all ages, produced leukemia only. The sarcoma cells were separated in tissue culture, and, when transplanted into rats, gave rise to sarcomas only. RBA-Sa released virus and induced sarcomas in chickens. Virus preparations from leukemic organs induced leukemia in 8 (11.2%) of 71 rats surviving 6-23 months. In chickens the same virus preparations caused tumors which, with two exceptions, regressed within 2 wk. Of the 203 rats inoculated with virus preparations from leukemic organs, about 50% died of hepatitis within 7-30 days. Among long-term survivors, 12 female rats developed 23 large mammary fibroadenomas.

- 2599 ULTRASTRUCTURAL LOCALIZATION OF SV40 VIRAL DNA IN CELLS, DURING LYTIC INFECTION, BY *IN SITU* MOLECULAR HYBRIDIZATION. (E.) Geuskens, M. (Inst. Sci. Res. Cancer, Villejuif, France) and E. May. *Exp Cell Res* 87(1):175-185, 1974.

The *in situ* molecular hybridization was combined with electron microscopy to detect simian virus 40 (SV40) in permissively infected monkey kidney cell cultures. Labeled SV40 complementary RNA (cRNA) was allowed to hybridize with the viral DNA for 20, 30, or 44 hr. In the 20-hr infected cultures, the amount of label localized over the nucleoplasm of most cells was

greater than in the same cellular compartment in the control cells; some label was localized over regions when the chromatin was more condensed. Most of the nucleoli were hypertrophied, and a preferential localization of label over the nucleoli was frequently observed. The ultrastructural aspect of the nucleoplasm and nucleolus of the 30-hr infected cells did not differ significantly from that of the 20-hr infected cells, although several nuclei contained many viral particles dispersed in the nucleoplasm. Label was often observed over regions of more condensed chromatin. In the 44-hr infected cultures, the nucleoplasm of most cells contained large zones filled with virus particles. Label was frequently observed over chromatin clumps which persisted between these zones, although the areas with virus particles were not labeled. The data suggest an important role of the host cell nucleolus during the lytic infection with SV40.

- 2600 PAPOVA VIRUS ETIOLOGY OF HUMAN LARYNGEAL PAPILLOMA: ELECTRON MICROSCOPE STUDY. (Ger.) Solisch, P. (Friedrich Loeffler Inst., Riems, Germany), H. Hahnefeld and R. H. Brandt. *Z Erkr Atm* 138:379-384, 1973.

By electron microscopy using negative contrast technique, papova virus was detected in human juvenile and adult papillomas of the larynx and in calf kidney cultures infected with such tissues. Papova viruses are regarded as the prototype of oncogenic viruses, and the papillomas induced by them are regarded as precancerous. Papova virus is very likely to constitute the etiological factor of laryngeal papilloma.

- 2601 SURFACE BIOCHEMICAL CHANGES ACCOMPANYING PRIMARY INFECTION WITH ROUS SARCOMA VIRUS. I. ELECTROKINETIC PROPERTIES OF CELLS AND CELL SURFACE GLYCOPROTEIN:GLYCOSYL TRANSFERASE ACTIVITIES. (E.) Bosmann, H. B. (U. Rochester, Sch. Med. Dent., N.Y.), K. R. Case and H. R. Morgan. *Exp Cell Res* 83(1):15-24, 1974.

Both chick embryo fibroblasts (CEF) and CEF transformed by the Schmidt-Ruppin strain of Rous sarcoma virus (SR-RSV) contain glycosyl ectoenzyme systems. Both the glycoprotein:glycosyl transferase and acceptors appear to be located on the external plasma membrane of both cell lines. The activity of the uridine diphosphate (UDP)-galactose and guanosine diphosphate (GDP)-mannose ectoenzyme systems was particularly high. Compared with the normal CEF, the activities of the UDP-galactose and GDP-mannose glycosyl ectoenzyme systems were elevated 12-fold. CEF infected with leukosis virus (RAV) or a temperature-sensitive RSV mutant (TS-68) at the nonpermissive temperature had glycosyl ectoenzyme levels similar to those of the normal CEF, suggesting that the elevations in the SR-RSV-infected cells were the result of transformation rather than merely viral infection. These glycosyl transferases and acceptors with activities expressible at the cell surface may be important in cell:cell adhesion and related phenomena or in the glycosylation of extracellular

glycoproteins. SR-RSV CEF in 0.0145 M NaCl, 0.6mM NaHCO₃, 4.5% sorbitol, pH 7.2, at 25 C had an electrophoretic mobility of $-2.45 \pm 0.02 \mu\text{m/s/V/cm}$, while control CEF had a mobility of $-2.04 \pm 0.01 \mu\text{m/s/V/cm}$. RAV-CEF grown at 37 C and TS-68 CEF grown at 41 C had mobilities of -2.03 and $-2.02 \mu\text{m/s/V/cm}$, respectively, indicating that the elevated electrophoretic mobility shown by the SR-RSV CEF was probably the result of viral transformation. The elevation in the electrophoretic mobility of the SR-RSV CEF was due primarily to elevated levels of surface N-acetylneuraminic acid and hyaluronic acid.

- 2602 FIBROMA REGRESSION IN RELATION TO ANTIBODY AND CHALLENGE IMMUNITY TO BOVINE PAPILLOMA VIRUS. (E.) Barthold, S. W. (Dept. Vet. Sci., U. Wisconsin, Madison) and C. Olson. *Cancer Res* 34(10):2436-2439, 1974.

Twelve neonate calves were repeatedly challenged (by intradermal inoculation and by scarification) with bovine papilloma virus (BPV). All calves were initially susceptible to BPV, and complete resistance to challenge occurred after the onset of fibroma regression. Fibroma regression was not correlated with serum antibody titers to BPV as measured by an immunodiffusion assay. Fibroma regression occurred prior to the onset of papillomatosis in eight of the calves. In the four calves that had later fibroma regression, after the onset of papillomatosis, the fibromas regressed, but fibropapillomas continued to grow progressively. The difference in susceptibility of calves is apparently due in part to the time of the onset of fibroma regression. Calves with early regression could be considered naturally resistant, as no tumor could be seen. The evidence presented in this study suggests that cell-mediated immunity is involved in BPV fibroma regression.

- 2603 THE PRESENCE OF THE EPSTEIN-BARR VIRAL GENOME IN HUMAN LYMPHOBLASTOID B-CELL LINES AND ITS ABSENCE IN A MYELOMA CELL LINE. (E.) Minowada, J. (Roswell Park Mem. Inst., Buffalo, N.Y.), M. Nonoyama, G. E. Moore, A. M. Rauch and J. S. Pagano. *Cancer Res* 34(8):1898-1903, 1974.

Nucleic acid hybridization between cellular DNA and complementary RNA to Epstein-Barr virus (EBV) was used to detect the presence of EBV DNA. Nineteen of 20 established human lymphoid cell lines studied contained EBV genomes in various amounts. The lines containing EBV DNA included five originating from tissues of patients with various diseases (Burkitt's lymphoma, malignant melanoma, myelogenous leukemia) as well as from healthy donors. The antibody titers to herpes group viruses in the donors and the presence of detectable EBV virion or associated antigens in the cell lines showed little if any correlation with the number of EBV genome equivalents in the established lymphoblastoid cell lines. However, large numbers of EBV genome equivalents were associated with the finding of virions by electron microscopy and of viral antigens by immunofluorescence. A unique cell line, RPMI 8226, derived from a patient

with multiple myeloma, did not contain detectable EBV genome. All 20 cell lines were identified as being of thymus-independent lymphocyte (B-cell) origin.

- 2604 SUPERINFECTION WITH ADENOVIRUS OF BURKITT'S LYMPHOMA CELL LINES. (E.) Faucon, N. (Virol. Unit, INSERM, Lyon, France), Y. Chardonnet, M. C. Perrinet and R. Sohier. *J Natl Cancer Inst* 53(2):305-308, 1974.

Two Burkitt's lymphoma cell lines, Epstein-Barr (EB) virus-positive Jijoye cells and EB virus-negative Raji cells, were infected with adenovirus type 5. Superinfection with adenovirus did not modify the growth of these cells. In the Jijoye cells, the adenovirus multiplication was cyclic; it was lower in the Raji cells, reaching a single maximum at 4 days. The production of intracellular hemagglutinating material followed the same pattern as infectivity. The presence of adenovirus in the nuclei of the superinfected Jijoye cells was confirmed by immunofluorescence and electron microscopy; the amount of virus in the Raji cells was low. Superinfection with adenovirus activated EB virus expression in the cells so that capsid antigen was enhanced in the EB virus-producing cells. EB virus did not prevent adenovirus multiplication.

- 2605 BIOLOGICAL PROPERTIES OF TWO STRAINS OF SIMIAN VIRUS 40 ISOLATED FROM PATIENTS WITH PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY. (E.) Narayan, O. (Johns Hopkins U. Sch. Med., Baltimore, Md.) and L. P. Weiner. *Infect Immun* 10(1):173-179, 1974.

The biological properties of two strains of simian virus 40 (SV40) derived from the brains of two patients with progressive multifocal leukoencephalopathy (PML) were compared with those of a standard laboratory strain of SV40. Like most strains of SV40, the infectivity of both SV40-PML viruses was resistant to treatment with chloroform, low pH, and maintenance at 50 C for 120 min. African green monkey kidney and BSC-1 cells were the best hosts for SV40-PML viral replication, and the cytopathology shown by these cultures was indistinguishable from that caused by the laboratory strain of SV40. Both SV40-PML viruses formed plaques in these cells; however, in the African green monkey kidney cells, strain 1 virus produced plaques measuring 2 mm in diameter, while strain 2 virus produced pleomorphic plaques from 1-10 mm in diameter. Hamster cells were not permissive for SV40-PML viral replication, infection resulting only in viral transformation. Inoculation of human fetal glial cells resulted in a permissive lytic infection of one cell type and a persistent infection with only partial expression of the viral genome in the other. No morphological evidence of transformation was obtained in the latter cells. Both strains of SV40-PML viruses were neutralized by commercial anti-SV40 serum, but in reciprocal kinetic neutralization tests difference in K values were noted when each was compared with the laboratory strain of SV40. Both SV40-PML viruses were oncogenic for ham-

sters, producing undifferentiated sarcomas when injected s.c. and choroid plexus papillomas after intracerebral inoculation. All hamster tumor cells contained intranuclear immunofluorescent tumor antigen. This was indistinguishable from SV40 T antigen in reciprocal staining reactions using hamster anti-T antibody induced by the two SV40-PML viruses and the laboratory SV40. Thus, the two human agents appear to be new variants of SV40.

- 2606 TRANSFORMATION OF NONHUMAN PRIMATE LYMPHOCYTES BY EPSTEIN-BARR VIRUS. (E.) Deinhardt, F. (Rush-Presbyterian-St. Luke's Med. Ctr., Chicago, Ill.), L. A. Falk and L. G. Wolfe. *Cancer Res* 34(5):1241-1244, 1974.

Continuous lymphoblastoid cell cultures were established from marmoset (*Saguinus* sp.), squirrel (*Saimiri sciureus*), owl (*Aotus trivirgatus*), and cebus (*Cebus apella*) monkeys after their peripheral lymphocytes were cultured with lethally, x-irradiated cells carrying Epstein-Barr virus (EBV). Simian lymphocytes were also transformed after exposure to infectious, cell-free EBV derived from some simian lymphoblastoid cell cultures. EBV-induced early, viral capsid, and membrane antigens; intranuclear inclusion bodies, and herpesvirus virions were demonstrable in most cell cultures. All cell cultures had B-cell characteristics; they produced immunoglobulins but did not form spontaneous rosettes with sheep erythrocytes. Four of six marmoset monkeys inoculated with EBV-transformed marmoset lymphocytes developed antibodies to Epstein-Barr viral capsid antigens; one marmoset inoculated with autochthonous transformed cells developed heterophile antibodies; and one of five marmosets inoculated with cell-free EBV developed a lymphoma. No overt clinical abnormalities were detected in any of the inoculated marmosets.

- 2607 EFFECT OF MURINE MILK SAMPLES AND HUMAN BREAST TISSUE ON HUMAN LEUKOCYTE MIGRATION INDICES. (E.) Black, M. M. (New York Med. Coll., N.Y.), D. H. Moore, B. Shore, R. E. Zachrau and H. P. Leis, Jr. *Cancer Res* 34(5):1054-1060, 1974.

Leukocytes from adult women with and without benign and malignant breast lesions were tested against cryostat sections of autologous and homologous benign and malignant (*in situ* and invasive) breast lesions. Simultaneous tests were made against RIII mouse milk samples that contain murine mammary tumor virus and against virus-free mouse milk samples from RIII and C57BL mice. Observations were also made on the response to a common environmental antigen (Varidase). The migration of leukocytes from breast cancer patients was commonly inhibited by Varidase but was not inhibited by virus-free mouse milk samples or by benign breast tissues. However, migration inhibition (> 25%) was found in 31% of breast cancer patients tested against RIII milk, in 33% of tests against homologous *in situ* breast cancer, in 29% of tests against autologous invasive breast cancer, and in 16% of tests against homologous invasive breast cancer tissues. Responsiveness to breast cancer tis-

sues was correlated with a high degree of cross-reactivity against RIII mouse milk. Conversely, leukocytes that responded to RIII milk cross-reacted in most of the tests against homologous *in situ* breast cancer and in approximately one-third of the tests against invasive breast cancer but were nonresponsive to RIII milk, C57BL milk, and benign breast lesions. It appears that the antigenicity of human breast cancer tissue is largely a reflection of a component that is similar to that found in murine mammary tumor virus-infected lactating mammary parenchyma.

- 2608 POLYAMINES IN NORMAL AND IN VIRUS-TRANSFORMED CHICK EMBRYO FIBROBLASTS. (E.) Bachrach, U. (Hebrew U.-Hadassah Med. Sch., Jerusalem, Israel), S. Don and H. Wiener. *Cancer Res* 34(7):1577-1580, 1974.

Cultures of normal and Rous sarcoma virus-transformed chick embryo fibroblasts were assayed for their RNA, protein, and polyamine content. Transformed cultures did not differ from normal ones in their protein and RNA content when grown under optimal conditions. Changing the growth medium resulted in a sharp increase in putrescine and spermidine levels in both normal and transformed cells. Transformation had no significant effect on cellular spermine levels, while a slight decrease in spermidine content was observed. On the other hand, putrescine levels were three to seven times higher in transformed cells than in normal controls, mainly in old primary cultures. The difference between normal and transformed cultures was most apparent in tertiary cultures when all the cells were transformed. There, the molar putrescine/spermidine ratio was 10 times higher in the transformed cells compared to the normal controls. This accumulation of putrescine may be explained by the previously reported increase in ornithine decarboxylase activity during tumor development.

- 2609 SYNTHESIS OF AVIAN ONCORNAVIRUS DNA IN INFECTED CHICKEN CELLS. (E.) Ali, M. (U. California, Sch. Med., Los Angeles) and M. A. Baluda. *J Virol* 13(5):1005-1013, 1974.

The intracellular synthesis and integration of viral DNA (vDNA) into the host cell genome was studied in cultured chicken embryo fibroblasts infected with avian sarcoma or leukemia viruses. The newly synthesized vDNA was detected by hybridization with 70S viral RNA. Extraction of infected cell DNA by the selective procedure of Hirt resulted in the enrichment of newly synthesized vDNA in the low-molecular weight supernatant fraction, leaving the bulk of the cellular DNA containing integrated vDNA in the high-molecular weight pellet fraction. This approach led to the detection of intracellular vDNA synthesis within 1 hr after infection and to the detection of vDNA integration into the cellular DNA within 24 hr. There was a several-fold increase in the vDNA content of the infected cells during the initial phase of virus infection. However, only a portion of this newly synthesized vDNA appeared to become covalently linked with the high-molecular weight cellular DNA. Most of the remaining unintegrated vDNA gradually

disappeared. The sedimentation profiles of minimally sheared cellular DNA in alkaline sucrose velocity gradients suggest that vDNA is synthesized as free linear molecules of approximately 3×10^6 daltons; these are subsequently covalently linked to the host cell DNA.

- 2610 BETA-GLUCURONIDASE RESPONSE OF CELLS INFECTED WITH ADENOVIRUS TYPES 5 AND 12.

(E.) Bardell, D. (Dept. Microbiol., U. New Hampshire, Durham) and T. G. Metcalf. *Infect Immun* 10(1):83-87, 1974.

To investigate the possible mechanism of membrane labilization caused by adenovirus type 12, but not adenovirus 5, the effect of these viruses on beta-glucuronidase, a representative hydrolytic enzyme normally found within cell lysosomes, was studied. Infection of an established line of chimpanzee liver cells with either nononcogenic adenovirus 5 or highly oncogenic adenovirus 12 under one-step growth conditions produced differing patterns of enzyme activity during the 48-hr period in which virus replication and changes in cell morphology occurred. There was an increase in total activity and enhanced leakage of beta-glucuronidase from the cells infected with adenovirus 12. However, the enzymatic pattern of the cells infected with adenovirus 5 was similar to that seen in uninfected cells. Hydrocortisone prevented the abnormal release of beta-glucuronidase from the adenovirus 12-infected cells. This compound had no effect on the total enzyme activity or on virus replication and the development of cytopathology. It is concluded that hydrolytic enzymes do not have a role in the production of distinctive adenovirus cytopathology.

- 2611 IMMUNOLOGICAL AND VIROLOGICAL INVESTIGATIONS ON OWL MONKEYS INFECTED WITH *HERPES-VIRUS SAIMIRI*. (E.) Pearson, G. R. (Natl. Cancer Inst., Bethesda, Md.), H. Rabin, W. C. Wallen, R. H. Neubauer, T. W. Orr and J. L. Cicmanec. *J Med Prim* 3(1):54-67, 1974.

The association between the induction of antibodies to early antigen (EA) and the detection of virus-infected peripheral blood lymphocytes, and the possible correlation of these factors with the response of lymphocytes to different mitogens, was investigated in owl monkeys infected with *Herpesvirus saimiri* (HVS). Sera from the monkeys were titrated for antibodies to EA and HSV-associated late intracellular antigens (LA). Although seven of 11 serum samples were positive for antibodies to LA, virus was recovered from the blood lymphocytes only when the serum samples were also positive for antibodies to EA. Increasing anti-EA titers reflected increasing numbers of virus-infected lymphocytes collected from the HVS-inoculated monkeys; this correlation was significant. There was no significant correlation between the number of virus-infected lymphocytes and the anti-LA titer. The loss of lymphocyte responsiveness to T-cell mitogens paralleled the induction of antibodies to EA and the recovery of virus from the blood lymphocytes, suggesting that virus genome-carrying lymphocytes were functionally altered.

2612 INDUCTION OF HEPATOCARCINOMA *IN VIVO* WITH FETAL MOUSE LIVER CELLS SPONTANEOUSLY TRANSFORMED IN CULTURE AND ISOLATION OF A TYPE C RNA VIRUS FROM THE CARCINOMA CELLS. (E.) Rhim, J. S. (Microbiol. Assoc., Inc., Bethesda, Md.), K. D. Wu, M. L. Vernon, H. W. Chen, H. Meier, C. Waymouth and R. J. Huebner. *Cancer Res* 34(3):484-490, 1974.

A hepatic cell line, FL83B/S2, derived from C57B/6J mice embryos, underwent spontaneous neoplastic transformation after long-term *in vitro* cultivation and produced progressively growing adenocarcinomas when inoculated s.c. into newborn isologous hosts. Transformation was accompanied by a conversion from murine leukemia virus group-specific antigen negativity to group-specific antigen positivity, and a type C RNA tumor virus was isolated from the tumors. This is the first report of type C virus isolation from murine hepatocarcinomatous cells.

2613 EPSTEIN-BARR VIRUS DNA IN HODGKIN'S DISEASE, AMERICAN BURKITT'S LYMPHOMA, AND OTHER HUMAN TUMORS. (E.) Nonoyama, M. (Sch. Med., U. North Carolina, Chapel Hill), Y. Kawai, C. H. Huang, J. S. Pagano, Y. Hirshaut and P. H. Levine. *Cancer Res* 34(5):1228-1231, 1974.

The association of Epstein-Barr virus (EBV) DNA in American tumors was tested by DNA-DNA reassociation kinetics and by complementary RNA hybridization. No detectable EBV DNA was found in Hodgkin's disease (5 patients) by DNA-DNA hybridization at the level of one EBV genome in every 20 or 50 cells. An association of EBV DNA with American Burkitt's lymphomas (3 cases) could not be demonstrated by complementary RNA hybridization at the level of one to two genomes/cell. One of six melanoma (biopsies) and two of seven carcinoma biopsies contained small but detectable amounts of EBV DNA. The very small number of EBV genomes/cell detected in the positive biopsies suggests that EBV may induce or initiate early steps of tumor formation, and that the virus may not be required for the development or maintenance of tumors.

2614 RELIABILITY OF THE RNA-DNA FILTER HYBRIDIZATION FOR THE DETECTION OF ONCORNAVIRUS-SPECIFIC DNA SEQUENCES. (E.) Shoyab, M. (U. California Sch. Med., Los Angeles), P. D. Markham and M. A. Baluda. *J Virol* 14(2):225-230, 1974.

Denatured DNA from leukemic myeloblasts or uninfected chicken embryos was immobilized on nitrocellulose filters and hybridized to a vast excess of ³H-70S RNA from purified avian myeloblastosis virus (AMV). The viral RNA was eluted from the RNA-DNA hybrids, purified, and then rehybridized in solution to an excess of either leukemic or normal embryonic chicken DNA. The results indicated that both the fast and slowly hybridizing virus-specific DNA sequences present in chicken cells can be detected and quantitated by the filter hybridization technique. The entire viral genome was hybridized to denatured leukemic DNA immobilized on filters, and the maximum amount of RNA hybridized by the leukemic and normal DNA was the same with the nonhybridized and eluted viral RNA.

The number of 28S chicken ribosomal genes determined by both methods of hybridization was 210 and 193 copies/chicken cell, resp. The number of 18S rRNA genes was estimated to be approximately 317 copies/cell genome by filter hybridization. Thus, filter hybridization can accurately detect DNA sequences present in relatively few numbers in the genome of higher organisms.

2615 EARLY AND LATE VIRAL-SPECIFIC POLYRIBOSOMAL RNA IN HERPES VIRUS-1 AND -2-INFECTED RABBIT KIDNEY CELLS. (E.) Murray, B. K. (Baylor Coll. Med., Houston, Tex.), M. Benyesh-Melnick and N. Biswal. *Biochim Biophys Acta* 361(2):209-220, 1974.

Virus-specific polyribosomal RNA was used to study the transcriptional control of herpes simplex virus type 1 (herpes virus-1) and type 2 (herpes virus-2) in rabbit kidney cells. Herpes virus-1-specific polyribosomal RNAs were isolated after infection of rabbit kidney cells at 37 C with a multiplicity of infection of 100. Herpes virus-2-specific polyribosomes, however, were not stable at this temperature and multiplicity of infection, a lower temperature (34 C) and lower multiplicity of infection (20-40) being required. Cytosine-β-D-arabinofuranoside was used to inhibit viral DNA synthesis to ensure that the early polyribosomal RNAs were transcripts of parental viral DNA. The presence or absence of cytosine-β-D-arabinofuranoside did not influence the synthesis of early viral-specific polyribosomal RNA of either virus. Both unlabeled early and late RNA effectively competed with ³H-labeled early RNA for complementary sequences in herpes virus-1 DNA, indicating that the RNA species transcribed early continue to be present late after infection. Competition between ³H-labeled late RNA and early RNA indicated a maximum homology of about 40% between the two RNA species. Similar results were found with herpes virus-2. Thus, the viral DNA transcripts synthesized in the nuclei of the cells are transported to the cytoplasm and are associated with the polyribosomes. There was no indication that the inhibition of viral DNA synthesis in rabbit kidney cells increased the level of viral DNA transcription.

2616 *IN VITRO* SYNTHESIS OF ADENOVIRUS CORE PROTEINS. (E.) Eron, L. (Natl. Inst. Child Health, Human Develop., Bethesda, Md.), H. Wesphal and R. Callahan. *J Virol* 14(2):375-383, 1974.

mRNA extracted from the polysomes of KB cells late during infection with adenovirus type 2 (Ad2) (Ad2 RNA) stimulated peptide synthesis in a cell-free system derived from Krebs II ascites cells; similar results were obtained with mRNA from polysomes of mock-infected cells (mock RNA). Prominent bands comigrating in sodium dodecyl sulfate (SDS)-polyacrylamide gels with virion polypeptides were synthesized only in response to Ad2 RNA. There was no discernible difference between the patterns of bands synthesized in response to mock RNA and the minus RNA control. Two of the polypeptides obtained in response to the Ad2 RNA corresponded to the adenovirus core protein V and the precursor to core pro-

tein VII. Identity between the virion capsid proteins and the *in vitro* synthesized polypeptides was established using SDS-hydroxyapatite chromatography, immunoprecipitation of the *in vitro* synthesized core protein pre-VII with antiserum directed against core protein VII, and tryptic peptide analysis of the *in vitro* synthesized core polypeptides.

- 2617 RNA VIRUS ASSOCIATED WITH HUMAN TRANSITIONAL CELL CANCERS OF THE URINARY TRACT. (E.) Fraley, E. E. (Dept. Urol., U. Minnesota, Minneapolis), A. Y. Elliott, P. Cleveland and N. Stein. *Minn Med* 57(11):871-875, 1974.
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2677 MOUSE MAMMARY TUMOR VIRUS RELATED RNA IN HUMAN TUMORS. (E.) Vaidya, A. B. (Inst. Med. Res., Camden, N.J.), A. S. Dion, M. M. Black and D. H. Moore. *Proc Am Assoc Cancer Res* 15(March):95, 1974.

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See also:

- * (Rev): 2407, 2408, 2412, 2423, 2427, 2429, 2437
- * (Immun): 2685, 2687, 2696, 2702, 2724, 2726, 2728, 2741, 2745, 2770, 2774, 2777, 2779
- * (Epid-Biom): 2832, 2834, 2847, 2852

2679 THE MURINE MALE ANTIGEN. III. VARIABLE EXPRESSION OF H-Y BY MURINE TUMORS. (E.)

Wikstrand, C. J. (U. North Carolina, Sch. Med., Chapel Hill) and G. Haughton. *J Natl Cancer Inst* 53(2):527-532, 1974.

A survey of primary and transplanted tumors which arose in male mice either spontaneously or after injection of 3-methylcholanthrene (MC), Moloney lymphoma virus, or Rous sarcoma virus established that the H-Y antigen is rapidly lost from or reduced in tumors in males. Two of five MC-induced tumors and one of two Rous virus-induced tumors expressed the male antigen but lost it within one to three transplant generations in syngeneic females. Three primary MC-induced sarcomas, two transplanted Moloney lymphomas, and one Rous virus-induced tumor never expressed the male antigen at a detectable level. This documented the rapid loss of a transplantation antigen from primary tumors. It is suggested that H-Y antigen loss is not a function of the primary neoplastic event, but rather a subsequent rapid antigenic simplification of the neoplastic cells.

2680 FAILURE OF CULTURED HUMAN T-CELL LYMPHOID LINES TO STIMULATE IN MIXED LEUKOCYTE CULTURE. (E.)

Royston, I. (U.S. Public Hlth. Service, Bethesda, Md.), P. R. Graze and R. B. Pitts. *J Natl Cancer Inst* 53(2):361-367, 1974.

Cultured human lymphoblastoid cell lines, originating from patients with acute lymphoblastic leukemia and possessing thymus-derived (T) lymphocyte characteristics, failed to activate normal allogeneic and xenogeneic (primate) peripheral lymphocytes in "one-way" mixed leukocyte cultures. In contrast, human and nonhuman primate lymphoblastoid cell lines, originating from normal donors and patients with leukemia or lymphoma and having bone marrow-derived (B) lymphocyte characteristics, were potent stimulators of autochthonous, allogeneic, and xenogeneic (primate) peripheral lymphocytes. T-cell lines may be derived from a clone of lymphoid cells which either lacked stimulatory antigens or lost such antigens during leukemogenesis.

2681 A FUNCTIONAL EXAMINATION OF HAPTEN-BINDING DERIVATIVES FROM A MURINE MYELOMA PROTEIN WITH IMMUNOGLOBULIN FEATURES. (E.)

Merz, D. C. (Dept. Pediatr., U. Minnesota, Minneapolis), G. W. Litman and R. A. Good. *Proc Natl Acad Sci USA* 71(5):1940-1944, 1974.

Various enzymatic derivatives of the murine myeloma protein IgA_{MOPC-315} were subjected to hapten-binding quantitation and circular dichroic analysis to ascertain the structural localization and functional definition of the immunoglobulin active site. The extrinsic Cotton effects observed with near saturation of the active site of the derivatives using *c*-dinitrophenyl-L-lysine were qualitatively and quantitatively identical when normalized with respect to their macromolecular content of dinitrophenyl-binding sites; ellipticity maxima of 378 and 438 nm and an ellipticity minimum of 325 nm were recorded.

Fluorescence quenching data confirmed the molecular nature of the derivation products of IgA_{MOPC-315} but also introduced disparity with respect to the binding kinetics, i. e., *K* values of 2.31×10^6 , 6.62×10^6 , and $2.06 \times 10^7 \text{ M}^{-1}$ were determined for IgA_{MOPC-315}, Fab'_{MOPC-315} and Fv_{MOPC-315} resp. These results can be explained in terms of possible modulating effects on hapten-binding contributed by novel conformations introduced through proteolysis.

2682 THE NATURE OF T AND B CELLS IN BLOOD LYMPHOCYTES IN HODGKIN'S DISEASE. (Ger.)

Cohnen, G. (Med. Clin. Polyclin., Essen, Germany), E. König, W. Augener, S. D. Douglas and G. Brittinger. *Verhandl Dtsch Ges Inn Med* 79:492-494, 1973.

The nature of T and B cells in blood lymphocytes in Hodgkin's disease was studied in an attempt to determine why cellular immunity is often depressed in Hodgkin's disease. Surface immunoglobulins were detected in isolated blood lymphocytes by a fluorescein-labeled IgG preparation of goat antiserum, while spontaneous rosette formation with sheep erythrocytes was studied with Jondal's method. Compared to control values of 15 to 40%, 17 to 55% of the lymphocytes from patients with Hodgkin's disease contained membrane immunoglobulin determinants. The percentage of rosette-forming lymphocytes ranged from 34 to 65% compared to 52-80% in the control. Consequently, the ratio of the T- to B-lymphocytes in patients with Hodgkin's disease was either normal or slightly shifted towards an increase in B-cells. A decrease in T-cells and corresponding increase in B-cells was observed primarily in patients subjected to radiation and/or cytostatic therapy. Thymidine incorporation *in vitro* following phytohemagglutinin and pokeweed mitogen stimulation of the lymphocytes was normal in two patients and reached its maximum on the 3rd and 5th day of culturing, resp. Normal reactions with delayed maxima were observed in two other patients. Both mitogens caused below-normal thymidine incorporation in other patients that were under cytostatic therapy at the time of the investigation.

2683 IMMUNE REACTIVITY OF LYMPHOID TISSUES ADJACENT TO CARCINOMA OF THE ASCENDING COLON.

(E.) Mavligit, G. M. (U. Texas, M. D. Anderson Hosp., Tumor Inst., Houston), A. V. Jubert, J. U. Gutterman, C. M. McBride and E. M. Hersch. *Surg Gynecol Obstet* 139(3):409-412, 1974.

The immunologic reactivity of lymphoid tissues neighboring carcinoma of the right colon was studied by the lymphocyte blastogenic response method in nine patients who had undergone right hemicolectomy for primary adenocarcinoma of the cecum or ascending colon. Positive blastogenic responses to phytohemagglutinin were observed in 22 of 25 lymphocyte preparations tested. Three of nine preparations derived from the terminal portion of the ileum gave a negative response, the magnitude of the positive response in the remaining six being significantly lower than in peripheral blood lymphocytes. The incidence and magnitude of the response was equal

for peripheral blood, appendix, and lymph node lymphocyte preparations. The blastogenic responses in mixed leukocyte reactions varied, peripheral blood lymphocytes and lymph node lymphocytes being highly reactive, and appendix lymphocytes and lymphocytes from the terminal portion of the ileum being less reactive or unreactive. The blastogenic responses to pokeweed mitogen and to streptolysin O were equally distributed except for terminal ileum lymphocytes where incidence of positivity and magnitude were lower than in other preparations. Among all preparations, the responses to streptolysin O were of less magnitude and less frequently positive than the responses to the mitogens. Tumor-induced blastogenesis among autologous lymphocytes were detected in 3/5 preparations from the terminal part of the ileum and in 2/5 peripheral blood lymphocyte preparations. Appendix lymphocytes and lymph node lymphocytes were totally unreactive to tumor cells. These different responses probably reflect different bone marrow derived and thymus dependent cell subpopulations and, in some instances, an immunosuppressive effect exerted by the tumor.

- 2684 RAT ALPHA-FETOPROTEIN: ISOLATION, CHARACTERIZATION AND ESTROGEN-BINDING PROPERTIES. (E.) Aussel, C. (Inst. Res. Sci. Cancer, Villejuif, France), J. Uriel and C. Mercier-Bodard. *Biochimie* 55(11-12):1431-1437, 1973.

Rat α -fetoprotein (α -FP) was isolated from amniotic fluid by an immunochemical procedure using high capacity immunoabsorbents. The yield was about 75% of the initial α -FP content. The isolated α -FP was pure, with a molecular weight of 72,000 daltons and a sedimentation coefficient of 4.5 s. Sucrose gradient sedimentation was used to demonstrate the binding activity of α -FP with estrone, estradiol, estradiol, and diethylstilbestrol. By equilibrium dialysis, the intrinsic association constant of pure α -FP was $1 \times 10^8 \text{ M}^{-1}$ for estrone and $6 \times 10^7 \text{ M}^{-1}$ for estradiol. One molecule of estrone and estradiol was bound per molecule of protein. No significant binding was observed with testosterone or progesterone. The specificity of the estrophilic activity of α -FP appears to be a characteristic of the protein. After electrophoresis of pure α -FP in acrylamide-agarose gels of low porosity, two closely migrating but distinct bands appeared. Both forms possessed estrogen-binding activity and common antigenic properties. The same molecular heterogeneity of α -FP was observed in whole amniotic fluid.

- 2685 CARCINOEMBRYONIC ANTIGEN AND HERPES ZOSTER AS DIAGNOSTIC AIDS IN MALIGNANT NEOPLASIA: REPORT OF A CASE. (E.) Burns, J. C. (Letterman Army Med. Ctr., San Francisco, Calif.). *Oral Surg Med Pathol* 38(3):372-377, 1974.

A 45-yr-old woman was referred to a dental clinic with facial pain and paresthesia of the lower lip. She was markedly obese, and had facial psoriasis, cranial alopecia, severe periodontitis, and breast masses of 5 yrs' duration. The diagnosis was herpes zoster, periodontitis, and periapical pathosis of

the lower right cuspid. The patient was treated surgically and examination of a biopsy specimen confirmed the diagnosis of herpes zoster. The patient continued to complain of severe pain in the lower right mandible. Clinical examination revealed a spontaneous ulcer of the mandibular right posterior edentulous ridge, with exposed bone. A biopsy specimen of the ulcer and adjacent bone was taken, after which the site failed to heal. The patient began to complain of pain in the lower right extremity and lower back, and within days was unable to walk. Examination of the biopsy specimen revealed malignant spindle-cell neoplasm. Further examination showed involvement of the right breast, lung, lymph nodes, spine, and liver, compromise to the right L5 nerve root. Serum carcinoembryonic antigen (CEA) levels were significantly elevated. The patient died after cardiopulmonary arrest a year later. This case is illustrative of the diagnostic value of herpes zoster and high serum CEA levels as indicators of immunologic alterations accompanying malignant neoplasia.

- 2686 THE DETECTION OF α_1 -FETOPROTEIN IN PATIENTS WITH VIRAL HEPATITIS. (E.) Silver, H. K. B. (Montreal Gen. Hosp., Quebec, Canada), J. Deneault, P. Gold, W. G. Thompson, J. Shuster and S. O. Freedman. *Cancer Res* 34(1):244-247, 1974.

The presence of α_1 -fetoprotein (AFP) in the sera of patients with acute viral hepatitis was investigated using a radioimmunoassay for AFP. Of the 128 adult patients studied, 40 had detectable levels of serum AFP at some time during the course of their illness. No relationship between seropositivity for hepatitis B antigen and AFP was noted in these patients. Investigation of a group of 24 patients, from whom serial samples were obtained over a period of greater than two weeks, demonstrated that the appearance of AFP was related to the severity of liver tissue destruction, as reflected by serum glutamic-pyruvic transaminase. It was found, however, that peak AFP levels were attained 5-16 days after peak glutamic-pyruvic transaminase levels.

- 2687 SPONTANEOUS INDUCTION OF ENDOGENOUS MURINE LEUKEMIA VIRUS-RELATED ANTIGEN EXPRESSING DURING SHORT-TERM *IN VITRO* INCUBATION OF MOUSE LYMPHOCYTES. (E.) Lonai, P. (Stanford U. Sch. Med., Calif.), A. Declève and H. S. Kaplan. *Proc Natl Acad Sci USA* 71(5):2008-2012, 1974.

Short-term lymphocyte cultures derived from mouse thymus, spleen, and lymph nodes were studied by immunofluorescence for the presence of murine leukemia virus group-specific antigens. The test made use of rat immune sera against syngeneic cells infected with the radiation leukemia virus or its pseudotype of murine sarcoma virus, and goat and rabbit antisera against purified murine leukemia virus group-specific antigen. Antigens reacting with these sera appeared in the cultured lymphocytes within 24 hr, and the proportion of immunofluorescent-positive cells increased to 25-80% by the second or

third day of cultivation; this was accompanied by a decrease in cell viability. The appearance of these antigens could be suppressed by inhibitors of DNA (mitomycin-C), RNA (actinomycin-D, cordycepin, and polyadenylic acid), and protein (cycloheximide) synthesis. No infectious virus could be detected by the immunofluorescence and XC-cell tests. This phenomenon appears to represent the spontaneous partial depression of endogenous murine leukemia virus replication in lymphocytes during short-term *in vitro* cultivation.

- 2688 THE CATABOLISM OF α_1 -FETOPROTEIN AND ALBUMIN IN RATS BEARING MORRIS HEPATOMA 7777. (E.) Sells, S. (U. California San Diego Med. Sch., La Jolla). *Cancer Res* 34(7):1608-1611, 1974.

The rate of catabolism of purified radiolabeled α_1 -fetoprotein (α_1 F) (t 1/2, 1.1 days) and albumin (t 1/2, 2.2 days) is the same in normal Buffalo rats with a mean α_1 F serum concentration of 0.054 μ g/ml and in rats bearing 2- to 5-g tumors of Morris hepatoma 7777 that have a mean serum concentration of 46 μ g/ml, almost 1000 times normal. A decreased rate of catabolism of both α_1 F (1.3 days) and albumin (3.2 days) is found in rats with large tumors (serum α_1 F concentrations, 7800 μ g/ml) just prior to death. The rising serum α_1 F concentration in hepatoma-bearing animals cannot be explained by decreased catabolism but is due to rapid synthesis by the hepatoma tissue. Because of the fast t 1/2 of one day, the serum α_1 F concentration accurately reflects the presence and condition of α_1 F-producing tumors in the rat.

- 2689 STUDIES CONCERNING THE REGIONAL LYMPH NODE IN CANCER. IV. TUMOR INHIBITION BY REGIONAL LYMPH NODE CELLS. (E.) Fisher, B. (U. Pittsburgh Sch. Med., Pa.), E. Saffer and E. R. Fisher. *Cancer* 33(3):631-636, 1974.

Tumor inhibition by regional lymph node cells (RLNC) was studied in two different syngeneic tumor-host systems: C3H mammary carcinoma and methyl-cholanthrene-induced tumors. *In vivo* neutralization and *in vitro* cytotoxicity experiments revealed that even after tumors had been present for a prolonged period, RLNC were capable of interfering with the growth of tumor cells. Neither distant lymph node cells nor spleen cells ever fully displayed that characteristic. Only when animals approached death from the tumors did RLNCs demonstrate loss of their neutralizing capability. Inhibition of growth of tumor cells by RLNCs was not impaired for at least as long as two months following removal of primary tumors. Cells obtained at the same time from other sources failed to display such a capability. The findings are compatible with others which have indicated that RLNCs are unique from the rest of the lymphoreticular system insofar as the immunologic response of a host to its tumor is concerned. The RLNCs are of singular importance in the initiation and maintenance of tumor immunity and are probably of greater significance than they are in the production and preservation of immunity to tissue transplants.

- 2690 CROSS-REACTING TUMOR-ASSOCIATED ANTIGEN(S) AMONG CHEMICALLY INDUCED RAT COLON CARCINOMAS. (E.) Steele, Jr., G. (Wallenberg Lab., U. Lund, Sweden) and H. O. Sjogren. *Cancer Res* 34(8):1801-1807, 1974.

Lymphocytes from rats bearing primary or isografted colon carcinomas or from rats immunized with cultured colon tumor cells were consistently cytotoxic to multiple colon tumor target cells. The colon carcinomas were induced by three different chemical carcinogens (N-methyl-N'-nitro-N-nitrosoguanidine, 1,2-dimethylhydrazine, and 3,2'-dimethyl-4-aminobiphenyl). Tested lymphocytes were not cytotoxic to normal kidney, normal colon mucosa, or polyoma tumor target cells. Furthermore, no cross-reactivity could be detected between two colon carcinomas and either a mammary carcinoma or a fibroadenoma. Sera from three rats bearing primary colon tumors induced by two different chemical carcinogens blocked the lymphocyte-mediated cytotoxicity of all the primary colon effector cell-colon tumor target cell pairs tested. Sera from animals bearing a polyoma virus-induced sarcoma did not inhibit the cell-mediated immunity in the colon tumor system. Sera from rats bearing the primary colon carcinomas did not suppress the cytotoxicity of lymphocytes from polyoma tumor-bearing rats against polyoma tumor target cells. It is postulated that the chemically induced rat colon carcinomas tested share common tumor-specific surface antigen(s).

- 2691 INTERMOLECULAR HETEROGENEITY OF THE CARCINOEMBRYONIC ANTIGEN. (E.) Banjo, C. (Montreal Gen. Hosp., Canada), J. Shuster and P. Gold. *Cancer Res* 34(8):2114-2121, 1974.

Studies were performed to determine the degree of heterogeneity within any one preparation of purified carcinoembryonic antigen (CEA) of the human digestive system and the variations in chemical composition between such preparations. Individual batches of CEA, isolated from hepatic metastases arising from adenocarcinomas of either the colon or stomach, were examined by a number of physicochemical and immunochemical parameters. Among the differences observed were the carbohydrate/protein ratio and the quantities of the individual amino acid and monosaccharide residues in the different purified preparations examined. These variations, in turn, were responsible for the secondary manifestations of heterogeneity observed upon gel electrophoresis. The polydisperse nature of the electrophoretic pattern of each of the purified CEA preparations upon alkaline polyacrylamide gel electrophoresis was largely due to variations in the sialic acid content of individual CEA molecules. In addition, the molecular size and antigenicity of the CEA varied, to some degree, from preparation to preparation. Nevertheless, colon tumors as a group were far more similar to one another than they were to the gastric tumor preparation studied. The observations demonstrate the overall complexity of the structure of the CEA molecule obtained from different sources, but also serve to elucidate certain of the parameters by which this molecular moiety may be defined.

- 2692 OVARIAN TUMOR-SPECIFIC ANTIGENS. (E.) S. Knauf (Dept. Obstet. Gynecol., U. Toronto, Canada) and G. I. Urbach. *Am J Obstet Gynecol* 119(7):966-970, 1974.

The tumor-specific antigens of human ovarian tumors were studied using samples of human serous cystadenocarcinoma (SCA), mucinous cystadenocarcinoma (MCA), solid epidermoid carcinoma of the ovary (SEC), and normal ovarian tissue (NO). Unabsorbed anti-SCA, anti-SEC, and anti-NO serum produced several immunodiffusion and immunoelectrophoretic precipitation arcs against normal tissue extracts, cancer tissue extracts, and normal human male and female serum. All of these precipitation patterns were complex, even though the immunizing antigens had been partially purified by perchloric acid (PCA) precipitation. Subsequent immunoelectrophoretic and immunodiffusion studies were performed using serum which had been sequentially absorbed with normal ovary and normal female serum. One of the SCA extracts contained four antigens or antigen families: two were neutral, one anionic, and one cationic. The anionic antigen was also present in the other SCA extract and in MCA extract. The two neutral antigens were also present in the SEC extract. None of these antigens was present in normal ovary or normal human serum. The cationic and anionic antigens of the first SCA extract carried at least one antigenic determinant which was also carried by one of the neutral antigens. The data indicate a definite relationship between the tumor antigens of the three types of human ovarian carcinoma.

- 2693 INCREASED IMMUNOGENICITY OF TSTA ON HETERO-KARYOXYTES OF SYNGENEIC TUMORAL AND ALLOGENEIC NORMAL CELLS. (E.) Barbanti-Brodano, G. (Inst. Microbiol., U. Bologna, Italy), A. T. Di Marco, L. Possati, C. Franceschi and G. Prodi. *Experientia* 30(8):947-950, 1974.

Fischer rat tumor cells were hybridized with normal Wistar rat embryo fibroblasts and the Mitomycin C-treated heterokaryocytes (predominantly polykaryocytes) injected s.c. into 2-month-old syngeneic rats. The animals were then challenged with liver tumor cells at different times after immunization. When the animals were immunized only once and challenged after a brief time interval, the hybrid cells induced a greater resistance to tumor growth than did a mixed population of nonfused tumor and normal cells. *In vitro* tests showed a substantial cell-mediated immunity in animals immunized with the hybrid cells, indicating that the presence of allogeneic and tumor antigens on the surface of the same cell increases the ability of tumor specific transplantation antigens to raise a cell-mediated reaction. When animals were immunized twice and challenged after a long time interval, the hybrid cells induced a low degree of resistance, the tumor incidence being close to that of nonimmunized controls. This effect was probably due to blocking rather than to a decreased immunogenicity of hybrid cells. Tumor cells "fused to themselves" induced a complete anti-tumor resistance. The data confirm the importance of the balance between cell-mediated and humoral immunity in the host response to tumors.

- 2694 CHILDHOOD LYMPHOBLASTIC LYMPHOMA, A CANCER OF THYMUS-DERIVED LYMPHOCYTES. (E.) Kaplan, J. (Child Res. Ctr. Michigan, Detroit), R. Mastrangelo and W.D. Peterson, Jr. *Cancer Res* 34(3):521-525, 1974.

Populations of tumor cells obtained from children with lymphoblastic lymphoma were compared with tumor cells from children with acute lymphoblastic leukemia for thymus- or bone marrow-derived lymphocyte characteristics. Thymus derived lymphocytes were identified by their ability to bind sheep RBC as rosette-forming cells. Bone marrow-derived lymphocytes were identified either by the presence of complement receptors or by the presence of immunoglobulins on their surface. Similar comparison was made between the thymus- or bone marrow-derived lymphocyte properties of lymphocyte cell lines established from children with lymphoblastic lymphoma and those established from patients with other lymphoproliferative diseases. The results obtained support the notion that childhood lymphoblastic lymphoma is a cancer of thymus-derived lymphocytes and is clearly different in origin from acute lymphoblastic leukemia.

- 2695 SPECIFIC INHIBITION OF LYMPHOCYTE BLASTOGENIC RESPONSES TO MITOGENS BY A FACTOR PRODUCED BY CULTURED HUMAN MALIGNANT LYMPHOMA CELLS. (E.) Hersh, E. M. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.) and B. Drewinko. *Cancer Res* 34(1):215-220, 1974.

A glass-adherent human lymphoma cell line (derived from the abnormal lymph node of a patient with the lymphocytic type of malignant melanoma) was found to produce an inhibitor of human *in vitro* lymphocyte blastogenic responses. The responses to mitogens, antigens, and allogeneic leukocytes were inhibited over 90%, as assayed by DNA synthesis or morphology. The effect was not associated with cytotoxicity and was reversible by washing the inhibited cells. The material was a nondialyzable, heat-stable protein. Its activity was not affected by DNase and RNase but was destroyed by Pronase. The inhibitor was species and tissue specific; it did not inhibit mouse lymphocytes or a variety of human tissue culture cell lines. The relationship of this material to regulation of lymphoid function and to the etiology and pathogenesis of cancer is discussed.

- 2696 VARIATIONS OF CYTOTOXIC ANTIBODIES TO CELLS WITH HERPES SIMPLEX VIRUS ANTIGENS IN WOMEN WITH PROGRESSING OR REGRESSING CANCEROUS LESIONS OF THE CERVIX. (E.) Thiry, L. (Inst. Pasteur du Brabant, Belgium), S. Sprecher-Goldberger, Y. Fassin, I. Gould, C. Gompel, J. Pestiau and F. de Halleux. *Am J Epidemiol* 100(4):251-261, 1974.

Antibodies to *Herpes simplex* virus antigens were studied for 3-30 months in 126 women at a Belgian center for the early detection of cancer. Neutralizing antibodies to *Herpes simplex* type 2 virus (HSV-2) did not vary in 96% of the women with normal cervix.

vical smears, and complement-dependent cytotoxic antibodies to HSV-2-infected hamster cells were stable in 81% of these women. Variations were common among women with pathological smears and the two types of antibodies often did not vary in a parallel direction. Of 18 women with progressing cervical lesions, 89% had high or increasing neutralizing antibody titers and 83% had decreasing or no serum cytolytic activities. Of 60 women who were treated for cervical carcinoma, or who had apparently been spontaneously cured of dysplasia of carcinoma *in situ*, 60% showed an increased cytolytic activity after treatment or when the cervical smear spontaneously became normal; only 15% of these women showed an increase in neutralizing antibodies. Sera plus complement assayed on an HSV-2-transformed hamster cell line had lower cytolytic activities than on HSV-2-infected cells, but the variations in activity were generally parallel in the two cell cultures. The data confirm previous indications that neutralizing antibody titers are related to the evolution of precancerous and cancerous lesions of the cervix. They are also in agreement with reports on other tumors which show that the antibodies to surface antigens vary inversely with the severity of the lesions.

- 2697 T AND B LYMPHOCYTE MEMBRANE MARKERS IN CELLS FROM PATIENTS WITH LEUKEMIA AND LYMPHOMA. (E.) Mendes, N. F. (Sao Paulo Sch. Med., Brazil), C. C. Musatti and M. E. A. Tolnai. *Int Arch Allergy* 46(5):695-706, 1974.

Rosette formation of human lymphocytes with untreated sheep RBC (E) or sheep RBC treated with antibody and complement (EAC) may be employed as a marker of T and B lymphocytes. Cells from 16 patients with leukemia and from 18 with lymphoma were compared with normal lymphocytes in their ability to form E and EAC rosettes. The results were compared with the *in vitro* responses to phytohemagglutinin (PHA) and in mixed leukocyte reactions (MLR). A correlation was observed between the impaired responses to PHA and MLR and diminished percentages of cells having receptors for E or both E and EAC. It is suggested that the percentages of EAC and E rosettes may vary with the evolution of the disease. Determination of these membrane markers in the peripheral blood cells in various diseases, allied to the study of the responses to PHA and MLR, may constitute a useful tool in *in vitro* evaluation of B and T cell presence and function.

- 2698 *IN VITRO* ACTIVITY OF LYMPHOCYTES AND SERUM OF C3Hf/Bu MICE DURING THE GROWTH OF METHYLCHOLANTHRENE-INDUCED TUMOR AND ITS REGRESSION FOLLOWING LOCAL IRRADIATION (E.) Jurin, M. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.) and H. D. Suit. *Cancer Res* 34(4):672-678, 1974.

Development of lymphocyte and/or serum activity of C3Hf/Bu mice against transplanted, methylcholanthrene-induced fibrosarcoma during tumor growth was investigated using the *in vitro* cytotoxicity test. Following an initial increase in lymphocyte activity, it decreased fairly rapidly when the tumor volume

increased above 100 cu mm. The blocking factor was present in the serum of all tumor-bearing mice. The same assays were performed following irradiation of the tumor with a single dose of 2500-4500 rads. If the tumor regressed after irradiation, the activity of lymphocytes increased and the serum lost its blocking abilities. The growing tumor acted as a depressor in the animal tumor system by diminishing the strength of cell-mediated response and inducing production of the blocking factor.

- 2699 TUMOUR-BOUND IMMUNOGLOBULINS. THE FATE OF IMMUNOGLOBULIN DISAPPEARING FROM THE SURFACE OF COATED TUMOUR CELLS. (E.) Fish, F. (Dr. George S. Wise Life Sci Ctr., Tel Aviv U., Israel), I. P. Witz and G. Klein. *Clin Exp Immunol* 16(3):355-365, 1974.

This paper confirms results showing that TA3 mammary carcinoma cells coated *in vivo* with immunoglobulins lose some of the coat upon transfer to *in vitro* conditions. By labeling IgG isolated from the ascitic fluid of TA3 tumors it was found that the immunoglobulin coating TA3 cells is dynamically exchanged with immunoglobulin in the corresponding ascitic fluid. Some of the released immunoglobulin is in a degraded state as judged from the fact that most of the released material lost the antigenicity of intact immunoglobulin and has a lower capacity to precipitate with ammonium sulfate at 50% saturation. The degraded immunoglobulin has a higher binding efficiency to tumor cells, which may have an exceedingly important biological significance if it occurs also *in vivo*. Such degraded molecules may compete successfully with cytotoxic or opsonizing antibodies for antigenic determinants on the tumor cell.

- 2700 LONG-TERM ESTABLISHMENT OF A HUMAN PLASMA-CELL LINE DERIVED FROM A PATIENT WITH IgD MULTIPLE MYELOMA. I. REQUIREMENT OF A PLASMA-CELL-STIMULATING FACTOR FOR THE PROLIFERATION OF MYELOMA CELLS IN TISSUE CULTURE. (E.) Jobin, M. E. (Sch. Med., U. California, Los Angeles), J. L. Fahey and Z. Price. *J Exp Med* 140(2):494-507, 1974.

Cell line LA-49, derived from pleural fluid cells of a patient with IgD multiple myeloma, was established in culture and maintained for more than one yr. The D-myeloma protein produced in culture was similar to the serum D-myeloma protein in electrophoretic mobility and in delta- and lambda-chain antigens. The plasma cell tumor culture differed from numerous immunoglobulin-producing B-lymphoblastoid cell lines established in the same laboratory in: morphology, type of immunoglobulin produced (IgD vs IgM, IgG, and/or, rarely IgA), growth characteristics, and chromosomal features. A growth factor was needed for cell division and maintenance of culture viability. This factor was readily supplied by irradiated feeder layers of normal human fibroblasts or conditional media from fibroblast cultures. Preliminary characterization of this factor revealed it to be a protein with a molecular wt of approximately 150,000 daltons.

2701 ISOLATION OF A TUMOUR SPECIFIC ANTIGEN FROM A RAT HEPATOMA BY LIMITED β -GLUCOSIDASE DIGESTION OF TUMOUR CELL MEMBRANE. (E.) Bowen, J. G. (Cancer Res. Campaign Labs., U. Nottingham, England). *Biochem Soc Trans* 2(4):652-654, 1974.

An 'extra nuclear' membrane fraction was prepared from the 4-dimethyl-aminoazobenzene-induced D23 rat hepatoma by limited β -glucosidase digestion. The soluble extract was fractionated by DEAE-cellulose column chromatography. Hepatoma D23-specific antigenic activity was detected by the capacity of isolated fractions to neutralize the membrane immunofluorescence staining of viable hepatoma D23 cells by specific antibody in syngeneic immune serum. Two discrete peaks of material (I and II) significantly decreased the fluorescence index of the absorbed sera below the level of 0.30. The specificity of the antibody absorption by the β -glucosidase-released membrane fractions was confirmed by assaying their capacity to interact with antibody in sera from rats immunized with another hepatoma (D30). When the anti-(D30) serum was absorbed with Peak I material, there was no significant decrease in the membrane immunofluorescence staining with hepatoma D30 cells, while absorption of the antiserum with the hepatoma D23 Peak II material nonspecifically neutralized anti-(D30) antibody. The latter fraction contained free β -glucosidase activity.

2702 BIOPHYSICAL-IMMUNOLOGICAL ASSAY FOR RIBONUCLEIC ACID TYPE C VIRUSES. (E.) Olpin, J. (Flow Labs., Inc., Rockville, Md.), S. Oroszlan and R. V. Gilden. *Appl Microbiol* 28(1):100-105, 1974.

A biophysical and immunological method for characterization of RNA type C virus suspensions is described. The method provides a relationship to the total viral mass concentration of the particle titer, the group specific antigen titer and the UV absorbance (268 nm) of 2% sodium dodecyl sulfate digests. Data for murine, rat, feline, and hamster viruses are shown to be analogous within the test limitations. From these data, an assessment of the viral purity can be made, the structural integrity can be evaluated, an approximate molecular wt can be computed, and the mole ratio of group specific antigen can be determined.

2703 APPEARANCE OF α -FETOPROTEIN IN RAT SERUM DURING INDUCTION OF PRIMARY HEPATOMA WITH REGARD TO DEVELOPMENT OF HISTOLOGICAL CHANGES IN LIVER TISSUE. (E.) Dolezalova, V. (Cancer Inst., Brno, Czechoslovakia), J. Feit and M. Simickova. *Neoplasma* 21(4):381-393, 1974.

The relationship between α -fetoprotein and the development of histological changes in liver tissue was studied during induction of primary hepatomas with 0.06% 4-dimethylaminoazobenzene (DAB) in Lewis rats. Attention was focused on the histological analysis of oval cells and autoradiographic evaluation of ^3H -thymidine-labeled cells. α -Fetoprotein was detected in serum and tissue homogenate

by immunoelectrophoresis. One of the conspicuous features of a histological rearrangement of liver tissue was cellular hyperplasia with proliferation of oval cells followed by the formation of hyperplastic nodules in which glycogen-rich cells, and later tumor cells, proliferated. No correlation between the frequency of occurrence of oval cells and α -fetoprotein production was found in the pre-cancerous period. The induced primary hepatomas were predominantly of the mixed cholangiohepatoma type, in general not producing α -fetoprotein. Judged by its effect on α -fetoprotein synthesis, DAB is a weak carcinogen; judged by its effect on oval cell proliferation, DAB manifests properties similar to those of strong carcinogens from the azo dye series.

2704 IMMUNOFLUORESCENT STUDIES OF THE SEROLOGIC REACTIVITY OF PATIENTS WITH MALIGNANT MELANOMA AGAINST TUMOR-ASSOCIATED CYTOPLASMIC ANTIGENS. (E.) Wood, G. W. (U. Kansas Med. Ctr., Kansas City) and R. F. Barth. *J Natl Cancer Inst* 53(2):309-316, 1974.

Indirect immunofluorescent (IF) tests were done on acetone-fixed imprints of ten malignant melanomas with the use of sera from 48 patients with melanoma, 17 with other types of solid tumors, and 65 normal blood-bank donors. Only small differences in the percentage of positive reactions (36-47%) were obtained with the three groups of sera, and similar reactivity was observed with other malignant tumors. Despite this qualitative similarity in reactivity, there were significant quantitative differences distinguishing melanoma patients from normal individuals. The mean titer for melanoma patients was 310; for normal sera it was 18. Sera from eight melanoma patients with stage I (local) and stage II (regional) disease had a mean titer of 152 compared with a titer of 423 for 14 patients with stage III (metastatic) disease. This difference suggests a positive correlation between antibody titer and the presence of metastatic disease.

2705 NATURE AND SIGNIFICANCE OF THE ANTIGENS ASSOCIATED WITH HUMAN GASTROINTESTINAL TUMOURS. (E.) Burtin, P. (Inst. Sci. Res. Cancer, Villejuif, France). *J Clin Pathol [Suppl]* 27(7):115-118, 1974.

Carcinoembryonic antigen (CEA), a glycoprotein containing about 50% carbohydrates, has been found in all adenocarcinomas of the colon, rectum, pancreas, and stomach (with a few exceptions), and in some hepatomas. It is also present in the metastases of these neoplasms. CEA is found in the mucosa of the fetal colon and in some glands of the fetal gastric mucosa. CEA is localized at the apical pole of malignant epithelial cells and fetal mucosal cells; it is probably synthesized in the cytoplasm and then secreted through the cell membrane at the apical pole of the cell. In some cases, CEA is a membrane-associated antigen, although it does not have the properties of a membrane-associated tumor antigen. CEA is neither a cancer-specific nor organ-specific antigen. The degree of tissue differentiation and

inflammation influences the amount present in tissues. It is not certain whether the amount of CEA produced/cell is greater if the cell is cancerous. Nonspecific cross-reacting antigen (NCA), a glycoprotein containing about 40% carbohydrates, crossreacts with CEA and is neither cancer- nor organ-specific. NCA is situated at the excretory pole of the glandular cells and in intraluminal deposits, but it can be found much more frequently than CEA on cellular walls. Autoantibodies against CEA have not been consistently demonstrated in the sera of cancerous patients. It is suggested that studies of cell-mediated immunity look more promising than studies of CEA or of autoantibodies against CEA as a means for characterizing antigens of colon carcinoma in humans.

- 2706 SELECTIVE IMPAIRMENT OF CELL ANTIGENICITY BY FIXATION. (E.) Gatti, R. A. (Karolinska Inst., Stockholm, Sweden), A. Ostborn and A. Fagraeus. *J Immunol* 113(4):1361-1368, 1974.

The effects of fixation by formaldehyde, *p*-formaldehyde, and glutaraldehyde on H-2^a and Moloney leukemia virus (MLV)-associated antigens were evaluated. Two cell types were employed: a) a MLV-induced lymphoma, YAC, which was passaged in ascites form in A/Sn mice or grown in long-term culture, and b) MLV-infected A/Sn and BALB/c mouse fibroblast monolayers. At low concentrations and short fixation periods, *p*-formaldehyde selectively impaired MLV antigens, preserving H-2^a. At high concentrations and longer fixation periods, *p*-formaldehyde markedly reduced H-2^a antigenicity while preserving MLV antigens. Fixation of either suspension cells or monolayers with glutaraldehyde (0.25% for 5 min at 20 C) markedly impaired both types of antigenicity.

- 2707 CORRELATION OF *IN VIVO* AND *IN VITRO* ASSAYS OF IMMUNOCOMPETENCE IN CANCER PATIENTS. (E.) Golub, S. H. (Dept. Surg., U. California, Los Angeles), T. X. O'Connell and D. L. Morton. *Cancer Res* 34(8):1833-1837, 1974.

Of 52 cancer patients studied for their *in vitro* response in lymphocyte blastogenesis assays, 50 were also studied for immunocompetence by *in vivo* assays. The *in vivo* assays were the delayed cutaneous hypersensitivity reaction to the primary stimulus of 2,4-dinitrochlorobenzene (DNCB) and the recall reactions to four common microbial antigens. The *in vitro* assays were the blastogenic response to three mitogens (phytohemagglutinin, pokeweed mitogen, concanavalin A) and the mixed lymphocyte culture (MLC) reaction. The carcinoma patients (14) demonstrated an apparent impairment of skin test reactions, but the least impairment of their lymphocyte blastogenesis reactions. The melanoma patients (29) had notable defects in lymphocyte function tests but less impairment of the skin test reactions. Results for sarcoma patients (9) were intermediate in both *in vivo* and *in vitro* assays. It is postulated that antigen recognition defects can exist in cancer patients that can be detected by the DNCB or MLC tests. Additionally, there may be lymphocyte proliferation defects demon-

strable in patients with certain histopathologies of cancer, especially melanoma, or in those in whom secondary immune responsiveness is impaired. These data suggest that the mitogen concanavalin A and MLC are probably more useful screening assays of *in vitro* immunocompetence than is the more commonly used mitogen, phytohemagglutinin.

- 2708 RENAL DEPOSITION OF SOLUBLE IMMUNE COMPLEXES IN MICE BEARING B-16 MELANOMA. CHARACTERIZATION OF COMPLEXES AND RELATIONSHIP TO TUMOR PROGRESS. (E.) Poskitt, P. K. F. (U. Louisville Sch. Med., Ky.), T. R. Poskitt and J. H. Wallace. *J Exp Med* 140(2):410-425, 1974.

Histologic and immunofluorescence studies of the kidneys of mice bearing a progressive melanoma show a proliferative glomerulonephritis associated with immune complex IgG deposition in the mesangium and along the glomerular basement membrane. This immune complex disease is distinct from the age-associated disease of the C57BL/6J host strain and the complexes are shown to consist of soluble tumor antigen and antitumor antibody. The intensity of IgG complex deposition correlates directly with tumor progress (size and metastases) and inversely with mononuclear leukocyte infiltration of the tumor. *In vitro* assay for lymphocyte cytotoxicity and humoral antibody were found to be less reliable indicators of tumor progress. The possible role of circulating soluble tumor antigen in modifying the immune response to tumors is illustrated in a schematic diagram.

- 2709 DYNAMICS OF α -FETOPROTEIN PRODUCTION COMPARED TO α_2 -MACROGLOBULIN DURING INDUCTION OF PRIMARY HEPATOMA WITH 4-DIMETHYLAMINOAZOBENZENE IN RATS. (E.) Dolezalova, V. (Cancer Inst., Brno, Czechoslovakia), M. Simickova, A. Kocent and J. Feit. *Neoplasma* 21(4):369-380, 1974.

Primary hepatoma was induced in Lewis rats with 4-dimethylaminoazobenzene administered in the diet during two time intervals: wk 1-17 and wk 29-36. α -Fetoprotein was followed in the serum as a marker of "acute phase" proteins. Detection and quantitative determination of these proteins was carried out by immunoelectrophoretic methods, using monospecific antisera. The proliferative activity of liver tissue was evaluated by measuring the rate of incorporation of ³H-thymidine into DNA. The presence of α -fetoprotein was observed in the two time phases as was an enhanced thymidine incorporation into liver DNA. α -Fetoprotein production fell abruptly after 50 wk and disappeared by the 54th wk. Subsequently, hepatomas appeared, but in the absence of α -fetoprotein production. In contrast, production of α_2 -macroglobulin showed a continuous rise, indicating a difference in mechanisms of biosynthesis of α -fetoprotein and of α_2 -macroglobulin. This distinction in mechanism appeared to have been made possible through the use of the weak carcinogen and of the fairly resistant strain of rats, a combination of factors which served to produce a more moderate course of carcinogenesis than that observed with other systems.

- 2710 TUMOUR-BOUND IMMUNOGLOBULINS. THE *IN VITRO* DISAPPEARANCE OF IMMUNOGLOBULIN FROM THE SURFACE OF COATED TUMOUR CELLS, AND SOME PROPERTIES OF RELEASED COMPONENTS. (E.) Ran, M. (Dr. George S. Wise Life Sci. Ctr., Tel Aviv U., Israel), F. Fish, I. P. Witz and G. Klein. *Clin Exp Immunol* 16(3):335-353, 1974.

Immunoglobulin-coated ascites tumor cells lose some of their immunoglobulin coat following transfer to *in vitro* conditions. The uncoating process is metabolism-dependent and related to the turning over of cell-surface components. Uncoated tumor cells bind globulin isolated from tumor eluates more efficiently than coated cells. Analysis of the spent medium of short-term tumor cell cultures revealed the presence of both immunoglobulin and antigenic cell surface components. It is not known whether the uncoating process occurs also *in vivo* but it is postulated that, since *in vivo* propagated tumor cells are found to be coated with immunoglobulin, either the immunoglobulin coat stays fixed on the cell *in vivo* or that an actively dynamic process is taking place in which immunoglobulin molecules leaving the cell are constantly replaced by other or by the same molecules.

- 2711 RABBIT ANTIBODIES TO NUCLEOLI OF NOVIKOFF HEPATOMA AND NORMAL LIVER OF THE RAT. (E.) Busch, R. K. (Dept. Pharmacol., Baylor Coll. Med., Houston, Tex.), I. Daskal, W. H. Spohn, M. Kellermayer and H. Busch. *Cancer Res* 34(9):2362-2367, 1974.

Antinucleolar antisera were produced in rabbits immunized with whole isolated nucleoli from normal rat liver and rat Novikoff hepatoma ascites cells. These antisera produced positive nucleolar fluorescence of varying degrees in nucleoli and nuclei. Tumor antinucleolar antisera produced strong nucleolar fluorescence with Novikoff hepatoma and Walker tumor, somewhat less with normal liver and even less with kidney. Liver antinucleolar antisera produced strong fluorescence with nucleoli of normal liver, Novikoff hepatoma and Walker tumor; fluorescence with kidney nucleoli was not so strong, but greater than with tumor antinucleolar antisera. Novikoff hepatoma and liver antinucleolar antisera fixed complement when combined with 0.15 M NaCl-soluble proteins extracted from the hepatoma and liver nucleoli. Nucleolar specificity of the antibodies was demonstrated by inhibition of fluorescence or complement-fixation following pretreatment of the immune sera with whole nucleoli or nucleolar 0.15 M NaCl-soluble protein fractions.

- 2712 INTERACTION OF IgE WITH RAT BASOPHILIC LEUKEMIA CELLS. IV. ANTIBODY-INDUCED REDISTRIBUTION OF IgE RECEPTORS. (E.) Carson, D. A. (Natl. Inst. Hlth., Bethesda, Md.) and H. Metzger. *J Immunol* 113(4):1271-1277, 1974.

Rat leukemic basophils with surface-bound IgE were reacted with fluoresceinated anti-IgE. The results were qualitatively similar to those obtained in analogous studies with lymphocytes, normal human baso-

phils, and other cells; local aggregation was only moderately temperature-dependent and was uninhibited by NaN_3 . Polar cap formation was significantly more sensitive to temperature and was completely inhibited by 0.01-0.1 M NaN_3 and cytochalasin B. The amount and rate of capping could be altered by varying either the number of bound IgE molecules or the anti-IgE concentration indicating that lattice formation is required for redistribution. No endocytosis of the antibody surface determinant complexes was observed. Under conditions adequate to inhibit cap formation on mouse lymphocytes, concanavalin A did not inhibit cap formation on the leukemic basophils.

- 2713 TUMOUR-CELL MUCOUS PROTEIN AND C.E.A. (E.) Rogalsky, V. Y. (P.A. Herzen Inst. Oncol., Moscow, USSR). *Lancet* (7882):729, 1974.

Two antigens have been detected in human colon tumors: carcino-embryonic antigen (CEA) and α -protein of mucus (α -PM). The distribution of α -PM differs among different tumors and in different parts of the same tumor. Much may be present in the cytoplasm, with less inside the vacuoles. In adenocarcinomas or polyps with no mucigen vacuoles, α -PM secretion may resemble that in merocrine glands. In some glands of undifferentiated carcinomas and adenocarcinomas, α -PM is present in the form of point-like vacuoles. In the cytoplasm of signet-ring cells, cytoplasmic fluorescence is significantly less intense. CEA appears to be the precursor of α -PM, a view which is supported by the fact that CEA appears at an earlier stage of development than α -PM.

- 2714 INTERFERON PRODUCTION BY LEUKOCYTE CULTURES FROM NEOPLASTIC PATIENTS. (E.) Cortada de la Pena, N. (Inst. Oncol., Buenos Aires, Argentina) and E. S. de Lustig. *Eur J Cancer* 10(3):189-192, 1974.

Interferon production by peripheral blood leukocyte cultures was studied in 37 patients with untreated solid tumors, four noncancer patients, and 20 normal donors. Interferon production was studied after infection of the leukocyte suspensions with Sendai virus at a multiplicity of infection of ten. The ability to produce interferon was reduced 2- to 16-fold in the leukocytes from the cancer patients compared with those from the noncancer patients and healthy donors; the average interferon titers induced in the cells from the cancer patients were 4.3 times lower than in the control cells. The lowest titers were obtained in patients with metastatic or undifferentiated infiltrating tumors. Immunostimulation with bacille Calmette-Guerin in one cancer patient increased his ability to produce interferon 2-fold. The interferon titer in a noncancer patient with erythematous lupus, an autoimmune disease, was reduced 4-fold compared with normal values. Serum blocking factors in cancer patients may hinder the ability of the leukocytes to receive viral stimulation for interferon production, or the inherent ability of lymphocytes or any white cells to produce interferon may be blocked or repressed in cancer patients.

- 2715 TUMOUR-BOUND IMMUNOGLOBULINS. THE *IN VITRO* FIXATION OF RADIOIODINE-LABELLED ANTI-IMMUNOGLOBULIN REAGENTS BY TUMOUR CELLS. (E.) Witz, I. P. (Dr. George S. Wise Life Sci. Ctr., Tel Aviv U., Israel), S. Kinamon, M. Ran and G. Klein. *Clin Exp Immunol* 16(3):321-333, 1974.

Radioiodine-labeled globulins from antisera directed against mouse immunoglobulin were fixed by cells of various mouse ascites tumors, indicating that the cells are coated *in vivo* with immunoglobulins. The amounts of tumor-bound immunoglobulin in the tumor-bearing animal increased as the time interval between tumor inoculation and the harvest of tumor cells increased. Seven days after transplantation in A mice, an average of about 10^5 IgG molecules coated each cell of a spontaneous mammary tumor (TA3). By day 10, the average amount of IgG/cell increased by a factor of three. Tumor cells from mice which had been irradiated prior to the tumor inoculation were associated, in general, with lower amounts of immunoglobulin than tumor cells from unirradiated mice.

- 2716 CHANGES IN THE HOMING PROPERTIES OF LABELED LYMPHOID CELLS CAUSED BY SOLID TUMOR GROWTH. (E.) Gillette, R. W. (Meloy Labs., Inc., Springfield, Va.) and C. W. Boone. *Cell Immunol* 12(3):363-369, 1974.

The effect of a progressively growing fibrosarcoma on the distribution of i.v.-injected ^{51}Cr -labeled cells from the lymph nodes, spleen, thymus, bone marrow, and Peyer's patches was measured in tumor-bearing BALB/c male and female recipient mice. Tumor presence caused a uniform depression of migration of labeled cells to the bone marrow. In most cases increased homing of cells to the spleen was also observed. Labeled cells prepared from lymph nodes and Peyer's Patches were generally unaffected by the presence of a growing tumor. Migration of labeled cells from tumor-bearing donors injected into normal syngeneic recipients suggests depletion or incapacitation of parts of the T-cell population of the spleen. These results emphasize the important relationship between splenic function and tumor progression.

- 2717 IMMUNOHISTOLOGIC STUDIES OF CARCINOMA OF THE PROSTATE. III. ELUTION OF INTER-EPITHELIAL ANTIBODIES FROM CARCINOMATOUS HUMAN PROSTATIC TISSUE FOLLOWING CRYOPROSTATECTOMY. (E.) Ablin, R. J. (Cook County Hosp. Grad. Sch. Med., Chicago, Ill.), M. J. Gonder and W. A. Soanes. *Oncology* 29(4):329-334, 1974.

Interepithelial antibodies reactive with autologous (human) and heterologous (monkey) prostatic tissue were demonstrated by indirect immunofluorescence in an eluate of carcinomatous prostatic tissue obtained at autopsy from a patient with metastatic adenocarcinoma of the prostate who exhibited remission of both his local prostatic malignancy and osteolytic lesions of the cervical spine following cryotherapy of his primary prostatic tumor. Elution of anti-

bodies from malignant prostatic tissue provided evidence of a preliminary nature that prostatic tissue (tumor?)-specific or tumor-associated antigens are liberated into the circulation following cryotherapy of the human prostate and offers further support to previous studies suggestive of the role of immunologic processes in prostatic cancer.

- 2718 QUANTITATIVE STUDIES ON TUMOR ENHANCEMENT IN MICE. I. ENHANCEMENT OF SARCOMA I INDUCED BY IgM, IgG1, AND IgG2. (E.) Rubinstein, P. (New York Blood Ctr., N.Y.), F. Decary and E. W. Streun. *J Exp Med* 140(2):591-596, 1974.

Male B6 mice were injected s.c. with a strain A fibrosarcoma maintained in the ascites form by serial passage in A/J mice and i.p. with purified immunoglobulins prepared from ascitic fluid of female B6 mice hyperimmunized with A/J spleen cells. Large (25-50 μg) doses of IgM inhibited tumor growth while lower doses caused enhancement. IgG2 in molar concentrations ~100-fold higher (600 μg) also suppressed tumor growth. Doses of 200 μg of either IgG2 or IgG1 resulted in enhancement. IgM combined with subenhancing doses of IgG1 or IgG2 had additive effects on tumor enhancement. IgG1, but not IgG2, suppressed the inhibitory effect of IgM in high concentrations. Determination of specific antibody content showed that 2×10^5 antibody molecules/injected tumor cell caused enhancement with the three immunoglobulins; 1×10^5 did so for IgG1 and IgM but not for IgG2.

- 2719 LYMPHOCYTE MEMBRANE MARKERS IN ACUTE LYMPHOBLASTIC LEUKAEMIA. (E.) Aiuti, F. (Inst. Clin. Med. III, U. Rome, Italy), G. Papa, V. Lacava, M. V. Ciarla, R. D'Amelio and J. Garofalo. *Br J Haematol* 27(4):635-641, 1974.

Peripheral blood lymphocytes from 18 5-36-year-old patients with acute lymphoblastic leukemia (ALL) (six previously untreated in the initial acute stage, two in relapse, and 10 in complete remission) were tested for spontaneous rosette formation with sheep red blood cells (E rosette), receptors for activated complement component (EAC), the Fc regions of certain immunoglobulin classes (FcR), and membrane immunoglobulins (mIg). The first test is specific for T cells, the latter three for B cells. The acute untreated cases of ALL are not characterized by a specific immunologic picture with respect to membrane markers. There is no one set immunological pattern of presentation, although in any one case there will be a definite reduction in all markers. The disease seems to present itself in a variety of selective deficiencies involving either predominantly T or B cells or both; the B cell pattern can be absent or within the extreme lower limits of normal, but the T cell population is always markedly reduced or absent. There is also an inverse relation between the percentage of peripheral blasts and membrane markers, which indicates that the blast cells are structurally and possibly functionally abnormal and are lacking markers of normal lymphocytes. In remission the

lymphocyte profile is normal with respect to membrane markers. Cultured lymphocytes derived from normal subjects have normal membrane markers characteristic of B lymphocytes, but cell lines from ALL patients have membrane characteristics of T lymphocytes.

- 2720 SEX-LINKED ATTENUATION OF THE GRAFT-VERSUS-HOST REACTION: EFFECT ON PATHOLOGIC FEATURES, INCLUDING TUMOR INDUCTION. (E.) Cornelius, E. A. (Dept. Diagnostic Radiol., Yale Sch. Med., New Haven, Conn.). *J Natl Cancer Inst* 53(3):759-762, 1974.

Male and female (C57BL/1 x SJL/J) F_1 mice were given injections of spleen cells from male SJL/J donors. The male F_1 recipients exhibited a typical graft-versus-host reaction (GVHR), with a 36% mortality by the 40th day; the F_1 females, by contrast, appeared healthy. Autopsy studies revealed severe pathologic changes characteristic of the GVHR in the F_1 males, as well as premalignant and lymphomatous changes in most of them. The F_1 females demonstrated only minimal evidence of a GVHR--there was slight lymphocytic depletion of the lymph nodes and spleen, with premalignant and lymphomatous changes in only a small proportion of the animals. The inhibition of a GVHR by a sex-related host-versus-graft reaction appears to be inversely related to the dose of spleen cells from male donors into female F_1 hosts.

- 2721 IMMUNITY IN THE TUMOR-BEARING HOST AND ITS MODIFICATION BY SERUM FACTORS. (E.) Baldwin, R. W. (Cancer Res. Campaign Labs., U. Nottingham, England), M. J. Embleton, M. R. Price and A. Robins. *Cancer* 23(4):1452-1460, 1974.

Tumor-bearing animals initiate immune responses to tumor-associated neoantigens. These responses are demonstrable by *in vitro* analyses of cell-mediated and humoral immune reactions, although it is emphasized that in most human studies, their correlation with positive tumor rejection reactions has not as yet been fully substantiated. Detection of cell-mediated immunity in tumor-bearing hosts has led to the concept that its effectiveness in controlling tumor growth may be modified or impaired by antagonistic humoral factors. This proposal is discussed with regard to the role of blocking reactions operative at the level of the target tumor cell, and with respect to direct inhibition of lymphocyte cytotoxicity by interaction with humoral factors. Available evidence indicates that blocking reactions are probably mediated by tumor-specific immune complexes, and although antibody-mediated blocking has been detected, its relevance in abrogating cell-mediated immunity in the tumor-bearing host is questionable. Alternatively, inhibition of the reactivity of sensitized lymphocytes, by tumor antigen or immune complexes, may prove to be of more importance in the immunologic control of tumor growth. The design of effective immunotherapy requires precise methods of assay of circulating tumor antigen, immune complexes and antibody in the subject of therapy.

- 2722 SOLUBLE MEMBRANE ANTIGENS OF HUMAN MALIGNANT MELANOMA CELLS. (E.) Hollinshead, A. C. (George Washington U. Med. Ctr., Washington, D.C.), R. B. Herberman, W. J. Jaffurs, L. K. Alpert, J. P. Minton and J. E. Harris. *Cancer* 34(4):1235-1243, 1974.

Delayed hypersensitivity reactions to soluble components of the cell membranes of autologous and allogeneic tumors were elicited in a series of patients with malignant melanoma. Two skin reactive antigens were prepared using stepwise low frequency sonication of cell membranes, chromatography of membrane sonicates on Sephadex G-200, and separation by polyacrylamide gel electrophoresis (PAGE). One group of antigens, in Sephadex fraction II, PAGE region a, appears to be melanoma-associated antigen. Sephadex fraction II, and further separated Sephadex fraction PAGE region a, produced no reactions in 21 of 22 tests in patients with cancers other than melanoma; positive reactions were seen in 17 of 22 patients with early stage melanoma and in 7 of 19 patients with late stage melanoma. The other antigen, PAGE region b from Sephadex fraction III, was also reactive in 5 of 6 early stage breast cancer patients. Comparable separated proteins from Sephadex fraction III PAGE region b, of normal black skin cell membrane sonicates were reactive in 4 of 9 early stage melanoma patients but were negative in 7 late stage melanoma patients. Sephadex fraction III and Sephadex fraction III PAGE region b produced no reactions in patients with renal, cervical, colonic, and head and neck cancer; 9 of 21 patients with early stage melanomas were skin test positive; positive reactions were seen in 13 of 18 patients with late stage melanoma. There may be blocking or interfering factors of intact membranes and of whole cell extracts to prevent the recognition of new specific or nonspecific proteins on the melanoma cell membrane. Reactivity to the separated antigens may reflect the presence of inhibitory or blocking factors in unfractionated materials which prevent skin reactivity.

- 2723 IMMUNOLOGIC STUDIES IN MALIGNANT LYMPHOMA: CORRELATION WITH HISTOLOGIC AND BONE-MARROW CHANGES. (E.) Srichaikul, T. (Dept. Med., Ramathibodi Hosp., Bangkok, Thailand), T. Siriasawakul, S. Wibulyachainunt, S. Khantanaphar, P. Matangkasombut, S. Sirisinha and C. Charupatana. *Am J Clin Pathol* 62(3):335-341, 1974.

The lymphocyte response to phytohemagglutinin (PHA), serum immunoglobulin levels, and cytology of bone marrow aspirates were determined for untreated patients with advanced malignant lymphoma (stages 3B and 4B): 26 patients had histiocytic lymphoma, 16 had lymphocytic lymphoma, and 20 had Hodgkin's lymphoma. Fifty-five percent (33) of the patients had decreased lymphocyte transformation with PHA (PHA-LT); six of the 33 patients had marked increases in the spontaneous transformation of lymphocytes cultured without PHA. A similar incidence of decrease PHA-LT was observed in histiocytic and lymphocytic lymphoma and Hodgkin's disease and in patients having primitive cell infiltration and lymphocytosis of the

bone marrow (58, 56, 45, 75, and 61%). The mean PHA-LT in each group was significantly lower than in a control group of 10 normal persons. Only 31% of the patients had nonspecific serum immunoglobulin changes without a definite pattern of monoclonal gammopathy. Thus, in advanced malignant lymphoma, abnormal PHA-LT appears to occur more frequently than serum immunoglobulin changes. The abnormal PHA-LT may reflect the bone marrow involvement with malignant cell clones at a late stage in the disease.

- 2724 ANTIBODIES TO EPSTEIN-BARR VIRUS-ASSOCIATED NUCLEAR ANTIGEN IN INFECTIOUS MONONUCLEOSIS. (E.) Henle, G. (Div. Virol., Children's Hosp., Philadelphia, Pa.), W. Henle and C. A. Horwitz. *J Infect Dis* 130(3):231-239, 1974.

Development of antibodies to Epstein-Barr virus-associated nuclear antigen (EBNA) was studied in 72 patients with heterophil antibody-positive infectious mononucleosis. In contrast to the early response of antibodies to Epstein-Barr viral capsid antigens observed in all patients and to the D component of Epstein-Barr virus-induced early antigens in 80% of the patients, antibodies to EBNA arose usually only one or more months after onset; in a few patients, however, these antibodies became detectable within three weeks. All patients eventually developed antibodies to EBNA. The geometric mean titer increased gradually, but even after 1 yr it did not match that in healthy donors. After primary infections, antibody to EBNA probably persists for life, since all donors with antibody to viral capsid antigen (some of them over 50 years old) showed antibody to EBNA. Conversely, no donor without antibody to viral capsid antigen had antibody to EBNA. The time of appearance of antibody to EBNA during infectious mononucleosis was unrelated to the severity of illness. It is suggested that EBNA becomes available from non-induced, EBV-transformed cells in a continuing process of their partial elimination by host defenses.

- 2725 ACUTE LEUKEMIA-ASSOCIATED ANTIGENS. (E.) Mann, D. L. (Immunol. Br., Natl. Cancer Inst., Bethesda, Md.), R. Halterman and B. Leventhal. *Cancer* 34(4):1446-1451, 1974.

Several investigators have demonstrated that antisera produced in heterologous animals by the injection of leukemia cells detect antigens associated with leukemia. Antisera were raised by injecting rabbits with cell membrane components from a lymphoid tissue culture cell line, Raji, derived from a patient with Burkitt's lymphoma. This antiserum is cytotoxic to acute myelocytic and acute lymphocytic leukemia cells. Control studies indicate that this reactivity pattern is not directed against histocompatibility antigens. Clinical studies demonstrate that this antigen appears at the time of the acute phase of the disease and disappears from the cell surfaces as the patients are induced into remission with chemotherapy. In addition, substances blocking the reactivity of this antiserum have been found in the sera of patients in the acute phase of their disease. Human embryonic

kidney cell lines do not express this antigen as detected by cytotoxicity and inhibition of cytotoxicity studies. However, when these cell lines are infected with the Rauscher leukemia virus, Kirsten virus, or the SV-40 virus, the cells transform and the antigen appears on the cell surface. The consequences of the detection of this antigen or antigens in relationship to the clinical diagnosis and treatment of this disease as well as to etiologic agents are discussed.

- 2726 RELATION OF HUMAN BLOOD-GROUPS MN TO CANCER CELL SURFACE ANTIGENS AND TO RECEPTORS FOR ONCOGENIC VIRUSES. (E.) Springer, G.F. (Evanston Hosp., Ill.) and P. R. Desai. *Ann Clin Lab Sci* 4(4):294-298, 1974.

Contrary to previous opinion, the human blood-group MN antigenic determinants are not the products of allelomorphic genes, rather, N is the precursor substance of M and the allelomorph to the M gene is amorph. The determinant structure of the N antigen is branched and possesses as nonreducing termini β -D-galactopyranosyl (Gal) and α -N-acetyl-neuraminic acid (NANA) linked to β -Gal. The M substance differs from N only in that α -NANA covers the terminal β -Gal of the N determinant. *Vicia graminea* anti-N reacts with terminal β -Gal of the N antigen as well as its precursor. A human blood-group N-like antigen has been found in the cell surface of the TA3 mouse mammary adenocarcinoma (ascites form). The TA3 cancer occurs as the nonstrain specific Ha subline and as the strain-specific St subline. This antigen reacts with *Vicia* anti-N. In serological specificity, the *Vicia* agglutinin is closely related to the Thomsen-Friedenreich anti-T agglutinin present in most human and animal sera. These sera plus complement kill over 95% of ordinary TA3-St cells and sialidase-treated Ha cells. Untreated TA3-Ha cells are fully resistant even though they absorb cytotoxin. Beta-galactosidase treatment of either Ha or St cells abolishes the killing activity of the sera. The cancer cells absorb anti-T but lose this capacity after exposure to β -galactosidase. An immunological cross-relationship between the human blood-group MN antigens and the receptor for the oncogenic avian subgroup B leukosis sarcoma virus has been observed.

- 2727 THE USE OF A RADIOIMMUNOASSAY FOR ALPHAFETOPROTEIN IN THE DIAGNOSIS OF MALIGNANCY. (E.) Waldmann, T. A. (Metabolism Br., Natl. Cancer Inst., Bethesda, Md.) and R. McIntire. *Cancer* 34(4):1510-1515, 1974.

Using a double antibody radioimmunoassay test, α -fetoprotein (AFP) was elevated (i.e., over 40 ng/ml) in 72% of patients with hepatocellular carcinoma, 75% of patients with teratocarcinoma or embryonal cell carcinoma of the testis, 23% of patients with pancreatic carcinoma, 18% of patients with gastric carcinoma, 5% of patients with colonic carcinoma, and 7% of patients with bronchogenic carcinoma studied. In contrast to these positive findings in patients with cancer, none of the 210 normal controls over one yr of age and only one of

the 300 patients with chronic nonhepatic diseases other than ataxia telangiectasia had elevated levels. All of 40 patients with the immunodeficiency disease, ataxia telangiectasia, had elevated AFP levels in accord with the view that these patients have a defect in organ differentiation. The radioimmunoassay for AFP was of special value in monitoring the effectiveness of therapy in certain forms of malignancy (e.g., hepatocellular carcinoma, embryonal cell carcinoma, and teratocarcinoma of the testis), since the product of a few tumor cells was detectable with this assay when AFP was undetectable as assessed by agar diffusion tests and when the residual tumor could not be detected by other clinical parameters.

- 2728 CONCORDANT SEGREGATION OF THE EXPRESSION OF SV40 T ANTIGEN AND HUMAN CHROMOSOME 7 IN MOUSE-HUMAN HYBRID SUBCLONES. (E.) Croce, C. M. (Wistar Inst. Anat. Biol., Philadelphia, Pa.) and H. Koprowski. *J Exp Med* 139(5):1350-1353, 1974.

Simian virus 40 (SV40) T-antigen positive cell clones were subcloned and analyzed for the expression of SV40 T antigen and for the presence or absence of human chromosome 7 as identified by Giemsa-banding staining. The original cell clones were derived from the hybridization of Lesch Nyhan SV40-transformed human fibroblasts deficient in hypoxanthine-guanine-phosphoribosyl-transferase (HGPRT⁻) with Cl-1D mouse cells deficient in thymidine kinase (TK⁻). Three of the 15 subclones of clone 52-58 Cl 19 (grown in hypoxanthine-aminopterin-thymidine medium) were T antigen positive; all contained human chromosome 7, while none of the T antigen negative subclones contained this chromosome. From clone 52-62 (1) Cl 5, grown in medium containing bromodeoxyuridine (BrdU), 9 subclones were examined, out of which 7 were found to be positive for T antigen. Similarly, from clone 52-62 (1) Cl 16, also in BrdU, 4 of 5 subclones were positive for T antigen. All of the T antigen-positive, and none of the T antigen-negative, cells contained human chromosome 7. Twelve of 20 triple hybrid clones between 52-62 (1) Cl 5 BrdU, and IR (HGPRT⁻) mouse cells were T antigen-positive and contained human chromosome 7; none of the T antigen-negative cells contained human chromosome 7. The results confirm the assignment of the SV40 T antigen gene to human chromosome 7 and rule out the possibility that the expression of the SV40 T antigen in SV40 T antigen-positive hybrid clones was caused by a transfer of the viral genome to a mouse chromosome.

- 2729 MALIGNANT TUMORS FOLLOWING KIDNEY TRANSPLANTATION. EXPERIENCES GAINED AT THE ZURICH TRANSPLANTATION CENTER. (Ger.) Wegmann, W. (Surg. Clin. A, U. Zurich, Switzerland), F. Largiader and U. Binswanger. *Schweiz Med Wochenschr* 104(23):809-814, 1974.

Of 139 kidney transplant patients who survived for more than four months following transplantation, four females and one male developed malignant tumors. Lymphoma and carcinoma of the bladder were found in 3 and 2 cases, resp. As of late 1973, the tumor in-

cidence in the kidney transplant patients amounted to about 3%. In each case the malignant lymphoma was classified as a reticulum cell sarcoma. Diffuse tumor involvement was found in one patient at autopsy. The brain and transplant were affected in another patient, and the brain alone in a third. One of the two patients with carcinoma of the bladder died of widespread metastases in abdominal lymph nodes, the peritoneum, liver, stomach, lungs, and prostate. In the other case, transformation of an initial differentiated papillary sarcoma into a solid sarcoma was observed. All patients were given immunosuppressive therapy with azathioprine, antilymphocyte globulin, prednisone and actinomycin D. The development of bladder tumors during immunosuppressive therapy may be related to prior abuse of acetophenetidin by these two patients. The two patients with malignant lymphoma had severe viral infections prior to tumor development: one had herpes zoster and the other herpes hominis with severe hypo- γ -globulinemia.

- 2730 ABSENCE OF B- AND T-CELL MARKERS ON ACUTE LYMPHOBLASTIC LEUKAEMIC CELLS AND PERSISTENCE OF THE T-CELL MARKER ON MITOGEN-TRANSFORMED T-LYMPHOCYTES. (E.) Collins, R. D. (Dept. Med., U. Cambridge, England), J. L. Smith, G. P. Clein and C. R. Barker. *Br J Haematol* 26(4):615-625, 1974.

Lymphocytes from six patients with acute lymphoblastic leukemia (ALL) were studied *in vitro* for thymus- (T-cell) and bone marrow-derived (B-cell) markers. The leukemic lymphoblasts did not form rosettes with sheep RBC (T-cell marker) or bear surface immunoglobulin determinants by indirect immunofluorescent staining (B-cell markers). The failure of the lymphoblasts to form rosettes was apparently not due to the fact that the lymphoblasts were in various stages of the cell cycle, as mitogen-transformed T-cells and T-cells in mitosis retained their capacity to form rosettes with sheep RBC. In contrast, leukemic B-cells, obtained from a patient with chronic lymphocytic leukemia and recognized by intracellular immunoglobulin crystals, did not form rosettes, nor did a small number of mitogen-transformed leukemic cells. Thus, lymphoblasts from some patients with the hematological picture of ALL do not have surface markers for either T- or B-cells. The hematological picture of ALL may be produced by lymphoid neoplasms not associated with a mediastinal mass, and less commonly by lymphoid neoplasms arising in the thymus.

- 2731 EVALUATION OF IMMUNOLOGICAL REACTIVITY IN BLADDER CANCER. (E.) O'Boyle, P. J. (Dept. Exp. Pathol., Cancer Res., U. Leeds, England), E. H. Cooper and R. E. Williams. *Br J Urol* 46(3):303-308, 1974.

Peripheral blood lymphocytes and serum from 69 male bladder cancer patients were tested for cytotoxic activity on T24 bladder cancer cells in tissue culture. The general range of cytotoxicity was small, and on repeated testing of the same patient and the same control, the variability factors were too great to allow direct comparisons between individual patients to be made. However, repeated test-

ing of the bladder tumor patients showed consistent cytotoxic activity in most samples, and patients who produced a cytotoxic response could be distinguished from those who did not. The highest cytotoxicity values were obtained in patients with well-differentiated, noninvasive lesions and those with multiple papillary tumors. A progressive decrease in both peripheral blood cell cytotoxicity and serum cytotoxicity was observed as the disease progressed. This was most noticeable in T1 and T4 lesions. When lymphocytes and serum from the same patient were added to the target cells, the serum was found to contain a reduction factor which decreased or abolished the cytotoxic effect produced by the lymphocytes alone. Noninvasive lesions showed 76% cytotoxicity in the presence of active disease, this being markedly reduced with dedifferentiation of cellular structure and invasion. However, all 3 patients with truly anaplastic tumors showed serum cytotoxicity, and 2 showed cellular activity.

- 2732 EFFECT OF DIFFERENT SERA ON GROWTH AND "SPONTANEOUS" NEOPLASTIC TRANSFORMATION OF MOUSE FIBROBLASTS *IN VITRO*. (E.) Carbone, G. (Natl. Inst. Study Cure Tumors, Milan, Italy), R. Piazza and G. Parmiani. *J Natl Cancer Inst* 52(2):387-393, 1974.

Murine fibroblasts undergo spontaneous malignant transformation when grown in calf serum (CS) and horse serum (HS), whereas this process is less frequent and delayed in fetal bovine serum (FBS). To test whether this effect is due to different growth-stimulating capacities of the different sera on murine fibroblasts, or to a selection by CS and HS of preneoplastic or early neoplastic cells, normal and spontaneously transformed BALB/c fibroblasts were cultivated for four days in Eagle's minimal essential medium with 0.5 or 10% FBS, CS, or HS. Tumor fibroblasts but not normal cells grew in the presence of 0.5% of the three sera. At 10% concentration, FBS, which in parallel experiments produced less spontaneous transformation than that produced by CS, stimulated growth of normal cells better than an equal concentration of CS and HS; however, the latter sera induced a more rapid growth of spontaneously transformed fibroblasts than of normal cells. Nine fibrosarcomas obtained by syngeneic backtransplantation of cell lines cultivated in CS and FBS were assayed for immunogenic properties by transplantation methods. The same was done with four sarcomas obtained by spontaneous neoplastic transformation *in vivo* of murine fibroblasts grown within cell-impermeable diffusion chambers kept in the peritoneum of mice for 420-460 days. Lack of immunogenicity was found in eight of nine *in vitro*-induced tumors and two of four *in vivo* counterparts, whereas the remaining three sarcomas had a significant degree of immunogenicity.

- 2733 T LYMPHOCYTES IN ASBESTOSIS. (E.) Kang, K. Y. (Natl. Kinki Central Hosp. Chest Disease, Sakai, Japan), Y. Sera, T. Okochi and Y. Yamamura. *N Engl J Med* 291(14):735-736, 1974.

The T-cell immunocompetence of patients with pulmonary asbestosis was evaluated. As compared with

the results obtained in five normal subjects the *in vitro* lymphocyte responses to phytohemagglutinin and the percentage of T cells in the blood lymphocytes were decreased in seven asbestosis patients; the intensity of the decrease paralleled the severity of the disease. Skin-reaction tests, which were performed with a purified protein derivative of tuberculin and phytohemagglutinin, showed a general depression in the seven asbestosis cases. The lymphocyte-transformation test appeared to be a more sensitive indicator than the skin tests or the ratio of T cells to total lymphocytes. The mean blood lymphocyte count was $2175/\text{mm}^3$ in 40 normal patients, $1499/\text{mm}^3$ in 29 patients with asbestosis, and $1100/\text{mm}^3$ in 10 patients with asbestosis and lung cancer. The data suggest some disturbances of the cellular immune mechanism and indicate that immunologic impairment may play a part in pulmonary fibrosis and in the development of neoplasms.

- 2734 INFLUENCE OF TUMOR SIZE AND SURGICAL RESECTION ON CELL-MEDIATED IMMUNITY IN MICE. (E.) Whitney, R. B. (Dept. Microbiol., U. British Columbia, Vancouver, Canada), J. G. Levy and A. G. Smith. *J Natl Cancer Inst* 53(1):111-116, 1974.

Tumor-specific immunity and general lymphoid cell competence were assessed in DBA/2J mice with 3-methylcholanthrene-induced transplantable tumors at various stages of development and after surgical resection. A significant level of tumor-specific immunity developed before palpable tumors were observed. The level of immunity increased slightly as tumors became palpable, then decreased, and finally disappeared completely when tumors were >10% of the total body wt. Resection rapidly increased the level of immunity. The response to both T- and B-cell mitogens decreased progressively with increasing tumor size but returned to normal levels after resection.

- 2735 PRIMARY LIVER CANCER, ALPHA₁ FETOPROTEIN AND HEPATITIS B ANTIGEN IN PAPUA NEW GUINEA. (E.) Woodfield, D. G., (Red Cross Blood Transfusion Service, Papua, New Guinea), Y. Endo and T. Matsuhashi. *Aust NZ J Med* 4(1):3-7, 1974.

Sera from 72 Papua New Guinean patients with hepatocellular carcinoma were tested for α_1 fetoprotein (AFP), hepatitis B antigen (HBAG) and antibody by sensitive techniques including radioimmunoassay. AFP was detected in 98% of samples and HBAG in 82%. The uniformity of immunological results might be related to a previously noted histological uniformity of the hepatic tumor types found in Papua New Guinea. It also suggests that a single etiological factor may be causing liver cancer in Papua New Guinea, possibly naturally occurring hepatotoxins and fungal contaminants of food, mainly aflatoxins. Hepatitis B antibody was present in only 2.8% of samples, suggesting an immune defect in liver cell cancer patients. The low level of HB antibody in patients with no detectable HBAG may indicate an immune reaction absorbing any antibody produced, and removing antigen from the sera.

(2736-2740)

2736 TRANSPLANTATION ISOANTIGENICITY OF A RAT SARCOMA AND ITS SPONTANEOUS METASTASES.

(E.) Proctor, J. W. (McGill U. Cancer Res. Unit, Montreal, Canada), P. Palmer and C. M. Rudenstam. *J Natl Cancer Inst* 53(2):579-580, 1974.

Two lung metastases, a lymph node metastasis, and the primary leg tumor from a single rat were assayed for antigen cross-reactivity by transplantation tests in the inbred strain of origin (Chester Beatty Hooded). The four tumor lines were implanted into the hind legs of groups of rats and excised eight days later to induce immunity. After 21 days these groups were challenged i.v. with the complete range of tumor lines. The incidence and weights of tumors in the lung were assayed later and a significant degree of cross-protection to i.v. challenge was observed among all tumor lines, regardless of which line had been used to immunize the animals.

2737 QUANTITATIVE RADIOIMMUNOASSAY OF IMMUNOGLOBULINS ON THE SURFACE OF HUMAN TUMOR CELLS. (E.) Jewell, W. R. (U. Kansas Med. Ctr., Kansas City) and E. C. Krishnan. *J Surg Res* 16(4): 424-427, 1974.

A technique for quantitatively measuring the immunoglobulins on the surface of tumor cells is described. Using indirect radioimmunoassay techniques, 460-1140 ng of immunoglobulins/10⁶ cells was found using a variety of tumor cells. Peripheral lymphocytes were also assayed for surface immunoglobulins, between 340 and 1045 ng/10⁶ cells being found. Cultured tumor cells, on the other hand, contained only negligible amounts of immunoglobulin. The test system is not specific for IgG in that it probably cross reacts with common light chains of other types of immunoglobulins. The physiologic importance of immunoglobulins on the surface of tumor cells is not revealed by this system.

2738 DETECTION OF CARCINOGEN-PROTEIN ANTIGENS IN SERUM FROM WORKERS EXPOSED TO ANILINE DYES. (Rus.) Korosteleva, T. A. (N. N. Petrov Inst. Oncol., Leningrad, USSR), A. P. Skachkov and I. I. Shvaidetskii. *Gig Tr Prof Zabol* (5):21-24, 1974.

Tests were carried out for circulating benzidine-protein antigens in the blood of 101 textile workers who were exposed to organic dyes. Benzidine-haptene was determined by diffusion reaction in agar gel, using rabbit immune sera against synthetic azoproteins prepared by reaction of diazotized-benzidine with horse serum proteins. Before use, the immune sera were absorbed with serum antigens of normal human blood donors. Female textile workers, 18 to 60 years of age, were divided into 5 groups: 1) contact only with direct dyes containing a benzidine radical; 2) contact with direct dyes not containing a benzidine group; 3) contact only with dyes not containing benzidine; 4) contact with dyes and other toxic substances such as acids, bases, chlorine, and soaps; 5) no contact with either dyes or toxic substances. Benzidine-haptene was detected in sera

of 25 of the 101 workers studied, and only in sera of workers who had contact with direct dyes containing this carcinogen radical. These findings, in combination with data on the etiological role of benzidine in occupational bladder cancer in man, may indicate a carcinogenic threat to workers in contact with direct dyes. The absence of the carcinogen in sera of certain workers exposed to direct dyes for more than 10 years suggests that immunological shifts occur, possibly as a result of formation of a neutralizing antibody.

2739 IMMUNOFLUORESCENT LOCALIZATION OF ALPHA-FETOPROTEIN SYNTHESIS IN ENDODERMAL SINUS TUMOR (YOLK SAC TUMOR). (E.) Teilum, G. (Inst. Pathol. Anat., U. Copenhagen, Denmark), R. Albrecht-sen and B. Norgaard-Pedersen. *Acta Pathol Microbiol Scand* [A] 82(4):586-588, 1974.

A radioimmuno-electrophoretic technique was used to measure the production of α -fetoprotein (AFP) in tissue sections from a pure endodermal sinus tumor (yolk sac tumor) removed from a 21-month-old boy. The serum AFP concentration was 2210 μ g/liter before surgery, 510 μ g/liter seven days after surgery, and 20 μ g/liter 63 days after surgery. The AFP concentration in the tumor homogenate was 3.8 μ g/g of tumor tissue. Immunofluorescence-microscopy revealed a positive AFP reaction in the cells lining the characteristic endodermal sinuses. A marked staining of intra- and extracellular periodic acid Schiff-positive, hyaline globules was also found. In both the cells and hyaline globules, the reaction varied in intensity. Thus, synthesis of AFP by the cells of the lining yolk sac endoderm account for the increased AFP concentrations in both the serum and tumor homogenate.

2740 SPONTANEOUS ANTILYMPHOMA REACTION OF PRE-LEUKAEMIC AKR MICE IS A NON-T-CELL KILLING. (E.) Gomard, E. (Cochin Hosp., Paris, France), J. C. Leclerc and J. P. Levy. *Nature* 250(5468):671-673, 1974.

The ability of AKR mice to develop a spontaneous T-killer cell response was studied with the chromium release test (CRT). A spontaneous antileukemic reaction was detected in 75% of 3- to 5-month-old (preleukemic) AKR mice, in 41% of nonleukemic mice older than 5 months, and in none of leukemic mice older than 5 months. The spontaneous reaction was not due to T cells since AKR spleen cells treated with C₃H anti- θ AKR serum and complement remained cytotoxic for the GL3 lymphoma of C57BL/6 mice. As a control, anti-C57BL/6 immune spleen cells from AKR mice were found to be able to develop a T-killer cell response against the GL3 lymphoma when treated with C₃H normal serum, with or without complement, or with anti- θ AKR serum without complement, while activity of the immune spleen cells was abolished by treatment with anti- θ serum plus complement. The spontaneous reactions of AKR spleen cells were decreased by column filtration and completely abolished by carbonyl iron, suggesting that the effector cells are macrophages. Activity was also suppressed by

trypsin, indicating that an antibody-dependent cell-mediated reaction is involved. The ability of pre-leukemic and older AKR mice to respond to allogeneic grafts suggests that their immune competence does not decrease with increasing age. It is hypothesized that the Rgv-1 gene which conditions the sensitivity to Gross virus-induced leukemia could be responsible for the AKR inability to develop an antileukemic T-killer cell response.

- 2741 ANTIBODIES TO EPSTEIN-BARR VIRUS, CYTOMEGALOVIRUS, AND AUSTRALIA ANTIGEN IN HODGKIN'S DISEASE. (E.) Langenhuisen, M. M. A. C. (U. Hosp. Groningen, Netherlands), T. Cazemier, B. Houwen, T. M. Brouwers, M. R. Halie, T. H. The and H. O. Nieweg. *Cancer* 34(2):262-267, 1974.

Indirect immunofluorescence assay showed that antibodies to Epstein-Barr virus and cytomegalovirus were significantly elevated in the sera of untreated Hodgkin's disease patients as compared with the sera of healthy age- and sex-matched controls. Significantly higher titers were also found in subgroups of patients with clinically advanced disease. This pattern did not hold for histologic subclasses, in that significant antibody elevations occurred only in the prognostically favorable types. Australia antibody was found by counter-electrophoresis in four of 25 patients and was absent from all of the controls. The prevalence of the various antibodies might be explained in terms of a humoral hyperreactivity secondary to a cellular immunologic deficiency. These results cast some doubt on the hypothesis of a specific role of Epstein-Barr virus in Hodgkin's disease.

- 2742 ORCHIDECTOMY AND THE IMMUNE RESPONSE. III. THE EFFECT OF ORCHIDECTOMY ON TUMOUR INDUCTION AND TRANSPLANTATION IN MICE. (E.) Castro, J. E. (Clin. Res. Ctr., Harrow, England). *Proc R Soc Lond [Biol]* 186(1085):387-398, 1974.

The effects of orchidectomy in Balb C mice on the induction and transplantation of tumors which are not obviously hormone dependent were studied. Orchidectomy prolonged the interval between s.c. injection of methylcholanthrene (5 mg/ml) and appearance of s.c. sarcoma. In tumor transplantation experiments orchidectomy conferred a slight but significant protective effect when methylcholanthrene-induced sarcoma cells (3.5×10^3) were grown in ascitic form; when the same cells grew as a solid s.c. tumor protection was increased. Protection was counteracted by s.c. administration of mouse anti-thymocyte serum (0.25 ml) and partially abrogated by thymectomy combined with orchidectomy, findings that suggest alteration of cell-mediated immunity as the mechanism of protection. Combination of cyclophosphamide treatment (200 mg/kg i.p.) with orchidectomy increased the antitumor effect of orchidectomy alone. In contrast, orchidectomy accelerated the appearance of spontaneous leukemia in AKR mice which is known to be thymus dependent. The explanation is probably that orchidectomy, by causing thymic hypertrophy increases the number of cells at risk of malignant transformation.

- 2743 ORGAN TRANSPLANTATION AND CANCER. (E.) Fortner, J. G. (Mem. Sloan-Kettering Cancer Ctr., New York, N. Y.) and M. H. Shiu. *Surg Clin North Am* 54(4):871-876, 1974.

Previously published data indicate that the risk of developing lymphoma is 35 times higher than normal after organ transplantation, this being almost entirely due to a risk of reticulum cell sarcoma which is 350 times greater than expected. The predilection of the reticulum cell sarcoma to involve the brain and spinal cord remains unexplained. The excess lymphoma risk appears within a yr of transplantation and persists at the same level for at least five or more yr. A less pronounced increase in the risk of epithelial cancers appears later in the post-transplantation period and becomes more pronounced with time. Cancers were diagnosed less than four months after transplantation in some patients with glomerulonephritis, an autoimmune disease. There may have been asymptomatic clinically occult tumors in the donor kidneys, but the presence of autoimmune disease is associated with an incidence of cancer that is higher than that of the general population. The risk of *de novo* cancer is probably less in liver transplant patients than in kidney cases. Patients with hepatic cancer do not have autoimmune disease, donor organs do not come from blood relatives, and the risk of spreading pre-existing neoplasms is probably less than that of kidney transplant patients. Organ replacement for malignancy is not necessarily followed by massive "wildfire" tumor growth. Following transplants of presumably healthy kidneys from persons who died of a variety of visceral cancers, many recipients developed clinically evident cancer in the transplanted organ, and many cancers metastasized. Cessation of immunosuppression after kidney transplantation was followed by tumor regression in three patients, but five patients succumbed. Although there is considerable evidence that currently used immunosuppressive drugs play a part in the development of such unusual cancers, immunosuppression in the absence of a transplant has not consistently caused an unusually increased risk of cancer. The clinical data in transplant cases support a viral activation hypothesis, which holds that viral oncogenesis is activated by immunosuppression along with the continued presence of a large mass of antigen, i.e., the allograft. The risk of this complication of transplantation is relatively small compared to the present indications for organ transplantation, and no cancer patient with fatal organ damage should be denied the benefits of organ transplantation for this reason.

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2787 DEFECTIVE T-CELL FUNCTION IN HODGKIN'S
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See also:

- * (Rev): 2403, 2405, 2410, 2411, 2415, 2418,
2419, 2440
- * (Chem): 2477, 2504
- * (Viral): 2573, 2575, 2581, 2602, 2607,
2611, 2629, 2639, 2640, 2642,
2658, 2659, 2663, 2668, 2671
- * (Epid-Biom): 2853

2788 ULTRASTRUCTURAL PECULIARITIES OF CANCER CELLS IN HUMAN BLADDER TUMORS. (Rus.)

N. T. Raihlin (Inst. Exp. Clin. Oncology, Moscow, USSR), A. S. Shubin and A. M. Romanenko. *Tsitologiya* 15(7):818-822, 1973.

Electron microscope studies were made of 22 transition-cell tumors of the urinary bladder (3 transition-cell papillomas, 6 highly differentiated transition-cell carcinomas, 6 medium differentiated transition-cell carcinomas, and 7 anaplastic tumors). The analysis of ultrastructural changes of the transitional epithelium and of the transition-cell tumors suggests that malignant degeneration involves structural changes in cell heterogeneity. The changes may result in ultrastructural rearrangement during which some cellular organoids grow simpler while others become more complex. Independent changes observed in various cancer cell organoids support the idea of tumor progression involving the progression on an ultrastructural level. Ultrastructural peculiarities of cancer cells may be used as criteria for evaluating the maturity of different transition-cell tumors of the urinary bladder.

2789 DIFFUSE COLONIC MUCOSAL HYPERPLASIA: MORPHOLOGY AND SIGNIFICANCE. (E.) Prior, J. T. (State U. New York, Upstate Med. Ctr., Syracuse) and E. Dunn. *Arch Surg* 109(4):575-577, 1974.

A 43-yr-old man was admitted to the hospital with a 6-month history of abdominal bloating and rectal bleeding. A well-differentiated adenocarcinoma surrounded by multiple small excrescences interpreted as hypertrophic mucosal changes was found along the posterior rectal wall. Discrete lymphoid nodules were associated with the majority of the hyperplastic foci, although some foci were unassociated with lymphoid tissue. Several submucosal nodules were observed which had no relationship to epithelial hyperplasia. Rare lesions seemed to fit the criteria for true polyps. They were generally of the adenomatous variety, although some were of the mixed variety. These polyps were invariably associated with mucosal lymphoid nodules. There was no evidence of benign polyps, hyperplasia, or lymphoid accumulations. While progression to cancer is not documented, the hyperplastic foci can apparently be traced in their evolution into adenomatous polyps.

2790 "EARLY" LARGE BOWEL CANCER: A MORPHOLOGIST'S DILEMMA. (E.) McCivitt, R. W. (U. Utah Med. Ctr., Salt Lake City). *Cancer* 34(3):904-908, 1974.

Among the problems involved in the detection of "early" colonic cancer is the question of the relationship of colonic polyps and villous tumors to the development of carcinoma. With some varieties of polyp, there is little disagreement as to their relationship to carcinoma. However, some have argued that a high colon cancer incidence in Gardner's syndrome and familial polyposis indicates a more general polyp-carcinoma etiologic relationship. Although an adenocarcinoma may arise in an adenomatous

polyp, invade its stalk, and metastasize, it appears to do so rarely. Most would agree that the evidence linking villous tumors to cancer is considerably stronger. The morphologist ordinarily has little difficulty distinguishing villous tumors from adenomatous polyps, but at times the distinction becomes less clear, particularly when there appears to be a discrepancy between the gross and microscopic morphology. Another related difficulty pathologists have with villous tumors is trying to predict from biopsy whether or not they contain cancer; carcinoma, if present, is usually focal and frequently central, obscuring it from both inspection and biopsy. Pathologists' efforts to find lesions often referred to as early or minimal cancers unrelated to some more obvious gross lesion have not been fruitful. A major difficulty is in finding, grossly, the appropriate area for study. Also, the ability to metastasize is not particularly size-dependent, so that when a pathologist looks at a small invasive colon cancer he cannot be certain that it is either early or minimal. In spite of certain technical problems, there appear to be situations in which cytology can serve as an important adjuvant to other diagnostic methods.

2791 EARLY MALIGNANT CHANGES IN PLEURAL PLAQUES DUE TO ASBESTOS EXPOSURE: A CASE REPORT. (E.) Lewinsohn, H. C. (TBA Industrial Products, Rochdale, England). *Br J Dis Chest* 68:121-127, 1974.

A Caucasian male began working at an asbestos textile factory in 1940 at the age of 33 yr. Until 1953 his job involved exposure to chrysotile asbestos dust and occasionally also to crocidolite. Medical examinations revealed rhonchi in his chest in 1957 and he began suffering from chronic bronchitis during the winter of 1958-59. In 1967 he developed symptoms of orthopnea and dyspnea on effort. He stopped smoking in 1960. He died in August 1970. Postmortem examination revealed congested and emphysematous lungs with no pulmonary fibrosis. The chest wall and visceral pleural surface contained many tumor nodules of varying size. Calcified plaques were present on the diaphragm and hyaline pleural plaques were seen on the chest wall. The diagnosis was mesothelioma due to exposure to asbestos. The tumors were classified as a tubulopapillary type of malignant mesothelioma. Asbestos bodies were found in the lungs and slight asbestosis was evident in places. This case illustrates the possible origin of a mesothelioma in noncalcified pleural plaques. All cases of pleural plaques should be officially registered to provide a basis for further prospective studies on the etiology of malignant pleural mesothelioma.

2792 THE PROBLEM OF PRELEUKEMIA. (Ger.) Bohnel, J. (Hanusch Hosp., Vienna, Austria) and A. Stacher. *Verhandl Dtsch Ges Inn Med* 79:415-416, 1973.

The initial stages of acute leukemia were studied with respect to pancytopenia. In 219 cases of acute leukemia, 22 cases of pancytopenia, 3 cases of mye-

loproliferative or lymphoproliferative syndrome, and 2 cases of polycythemia vera were identified as the initial stages of the disease. In patients with pancytopenia as an initial stage, toxic effects of radiation, drugs, synthetic resin varnishes and insecticides were demonstrated. Asthenia, susceptibility to infection, and hyperthermia were the initial symptoms preceding acute leukemia. Cell-rich or normal bone marrow were found in 15 cases and hypoplastic bone marrow, in 7 cases. The initial syndrome was anemia in one case, anemia with thrombocytopenia in 8 cases and pancytopenia in 11 cases. Anemia was always normocytic or macrocytic, and anisocytosis and poikilocytosis were found in the peripheral blood in almost all cases. Erythroblasts were present in the peripheral blood only in two cases. The reticulocyte count ranged from zero to 1.5%. Leukopenia was almost always characterized by granulocytopenia. Pseudo-Pelger cells were detected in 4 cases. The serum iron levels were above normal in 13 cases, normal in 7 cases, and below normal in 2 cases. Relative proliferation of the erythropoietic cells was demonstrated in 16 cases. Siderocytes and sideroblasts were found in 11 and 5 patients, resp. Erythroblasts positive to periodic acid-Schiff reagent were found in 2 cases. Morphological changes in the megakaryocytes were detected in almost all cases. The findings indicate that preleukemia should not be restricted to the cell-rich forms of pancytopenia.

- 2793 CLINICAL AND CYTOGENETIC INVESTIGATIONS OF PRELEUKEMIC STATES. (Ger.) Bauke, J. (Ctr. Internal Med. Pediatr., U. Ulm, Germany), H. Hoerler, S. Gienger and H. Heimpel. *Verhandl Dtsch Ges Inn Med* 79:419-422, 1973.

Clinical and cytogenetic investigations of preleukemic states are evaluated for seven patients who later developed leukemia. Preleukemic states consisted of pancytopenia (2 cases), anemia (4 cases) and polycythemia vera (1 case). Two cases of C-trisomy and one case of C-monosomy were detected. A preleukemic state was diagnosed which corresponded to Freireich's syndrome and involved refractory anemia, hyperplasia of the erythropoiesis, and C-monosomy in bone marrow cells. These findings and literature data indicate that patients with preleukemic conditions and abnormal clones in the bone marrow are especially inclined to develop leukemia.

- 2794 CHROMOSOMES AND MALIGNANCY. (E.) Jones, K. W. (No affiliation). *Nature* 252(5483): 525, 1974.

- 2795 ULTRASTRUCTURE OF OVARIAN TUMORS. (Pol.) Woyke, S. (Polish Acad. Med., Szczecin). *Patol Pol* 25(2):287-290, 1974.

- 2796 TRICHODISCOMA. A BENIGN TUMOR RELATED TO HAARSCHIEBE (HAIR DISK). (E.) Pinkus, H. (Wayne State U., Sch. Med., Detroit, Mich.), R. Coskey and G. H. Burgess. *J Invest Dermatol* 63(2): 212-218, 1974.

- 2797 LEIOMYOSARCOMA OF THE BREAST ORIGINATING FROM MYOTHELIUM (MYOEPIOTHELIUM). (E.)

Cameron, H. M. (Dept. Pathol., U. Nairobi, Kenya), H. Hamperl and W. Warambo. *J Pathol* 114(2):89-92, 1974.

- 2798 AN EXTRARENAL WILMS' TUMOR ARISING FROM A SACROCOCCYGEAL TERATOMA. (E.) Tebbi, K. (Washington U. Sch. Med., St. Louis, Mo.), A. H. Ragab, J. L. Ternberg and T. J. Vietti. *Clin Pediatr* 13(12):1019-1021, 1974.

- 2799 QUANTITATION OF HAEMOPOIETIC CELLS FROM NORMAL AND LEUKAEMIC RFM MICE USING AN IN VIVO COLONY ASSAY. (E.) Gordon, M. Y. (St. Bartholomew's Hosp., London, England). *Br J Cancer* 30(5):421-428, 1974.

- 2800 HISTOPATHOLOGY OF CYSTADENOMA OF THE OVARIES. (Pol.) Szamborski, J. (Acad. Med., Warsaw, Poland). *Patol Pol* 25(2):249-260, 1974.

- 2801 GERM CELL TUMORS OCCURRING IN DYSGENETIC GONADS (GONADOCYTOMAS). (Pol.) Teter, J. (Acad. Med., Warsaw, Poland). *Patol Pol* 25(2):213-236, 1974.

- 2802 THE MORPHOLOGY OF TUMOURS OF THE NASAL CAVITY AND THE OLFACTORY BULB OF THE RAT. (Ger.) Barbosa-Coutinho, L. (Max Plank Inst. Brain Res., Cologne, Germany), H. D. Mennel and K. J. Zulch. *Acta Neurochir* 31(1/2):73-88, 1974.

- 2803 ATYPICAL CILIA IN THE TRACHEOBRONCHIAL EPITHELIUM OF THE HAMSTER DURING RESPIRATORY CARCINOGENESIS. (E.) Harris, C. C. (Nat'l. Cancer Inst., Bethesda, Md.), D. G. Kaufman, F. Jackson, J. M. Smith, P. Dedick and U. Saffiotti. *J Pathol* 114(1):17-19, 1974.

- 2804 AN ELECTRON-MICROSCOPIC STUDY OF A SCHWANNOMA WITH SPECIAL REFERENCE TO BANDED STRUCTURES AND PECULIAR MEMBRANOUS MULTIPLE-CHAMBERED SPHEROIDS. (E.) Sun, C. N. (V.A. Hosp., Little Rock, Ark.) and H. J. White. *J Pathol* 114(1):13-16, 1974.

- 2805 CHOLANGIOCARCINOMA. A CLINICOPATHOLOGIC STUDY OF FIVE CASES WITH ULTRASTRUCTURAL OBSERVATIONS. (E.) Alpert, L. I. (Mount Sinai Sch. Med., City U. New York, N.Y.), F. G. Zak, S. Werthamer and J. F. Bochetto. *Hum Pathol* 5(6):709-728, 1974.

- 2806 PRIMARY INTRACRANIAL ADENOID CYSTIC CARCINOMA (CYLINDROMA). AN ELECTRON MICROSCOPIC STUDY. (E.) Willson, N. (Coll. Phys. Surg., Columbia U., New York, N.Y.) and M. Rosen. *Acta Neuropathol (Berl)* 29(1):85-90, 1974.

- 2807 CYSTIC ADENOMA OF A MINOR SALIVARY GLAND: A HISTOCHEMICAL STUDY. (E.) Harrison, J. D. (King's Coll. Hosp. Dent. Sch., London, England). *J Pathol* 114(1):29-38, 1974.
- 2808 AN OLIGOMERIC HYDROXYPHENYLALANINE IN MALIGNANT MELANOMA: A NEW TYPE OF MELANOGEN. (E.) Gruhn, W. B. (Dartmouth-Hitchcock Med. Ctr., Hanover, N.H.), J. S. Pomeroy and L. H. Maurer. *Biochem Biophys Res Commun* 61(2):704-709, 1974.
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- 2810 BIOLOGY OF TRANSITIONAL MALIGNANCY. (E.) Paulson, D. F. (Duke U. Med. Ctr., Durham, N.C.), R. A. Bonar, D. D. Mickey, J. Vergara, K. R. Stone and J. F. Glenn. *Trans Am Assoc Genitourin Surg* 66:121-125, 1974.
- 2811 FINE STRUCTURAL IDENTIFICATION AND ORGANIZATION OF THE EPIDERMAL PROLIFERATIVE UNIT. (E.) Allen, T. D. (Christie Hosp., Manchester, England) and C. S. Potten. *J Cell Sci* 15(2):291-319, 1974.
- 2812 LOBULAR CARCINOMA *IN SITU* OF THE BREAST WITH DUCTAL INVOLVEMENT. FREQUENCY AND POSSIBLE INFLUENCE ON PROGNOSIS. (E.) Andersen, J. A. (Sundby Hosp., Copenhagen, Denmark). *Acta Pathol Microbiol Scand [A]* 82(5):655-662, 1974.
- 2813 MALIGNANT CHANGES IN SEBORRHEIC KERATOSES. (E.) Kwitteken, J. (Mount Sinai Sch. Med., City U. New York, N.Y.). *Mt Sinai J Med NY* 41(6):792-801, 1974.
- 2814 HUMAN OVARIAN NEOPLASMS: LIGHT AND ELECTRON MICROSCOPIC CORRELATIONS. II. THE CLEAR CELL TUMOR. (E.) Salazar, H. (Magee-Womens Hosp., Pittsburgh, Pa.), L. P. Merkow, W. S. Walter and M. Pardo. *Obstet Gynecol* 44(4):551-563, 1974.
- 2815 CERVICAL CARCINOMA *IN SITU* AT AKRON GENERAL MEDICAL CENTER. THE VALUE OF COLONOSCOPY. (E.) Yates, W. T. (Akron Gen. Med. Ctr., Ohio) and W. A. Cook. *Ohio State Med J* 70(10):625-627, 1974.
- 2816 MORPHOLOGY AND AUTORADIOGRAPHY STUDIES OF GYNAECOLOGICAL TUMOURS IN ORGAN CULTURE. (E.) Siracky, J. (Cancer Res Inst., Bratislava, Czechoslovakia), J. Matoska and E. Siracka. *Neoplasma* 21(3):307-312, 1974.
- 2817 TUMORS OF NEURONS AND THEIR PRECURSORS. (E.) Feigin, I. (New York U. Med. Ctr., N.Y.) and G. N. Budzilovich. *J Neuropathol Exp Neurol* 33(4):483-506, 1974.
- 2818 JUVENILE FIBROMA OF ANTRAL ORIGIN. (E.) Ramanjaneyulu, P. (Kasturba Med. Coll. Hosp., Manipal, India). *Int Surg* 59(8):423-424, 1974.
- 2819 CHONDROSARCOMA: A LIGHT AND ELECTRON MICROSCOPIC STUDY. (E.) Erlandson, R. A. (Mem. Hosp. Cancer Allied Dis., New York, N.Y.) and A. G. Huvos. *Cancer* 34(5):1642-1652, 1974.
- 2820 LOCALIZED FIBROUS TUMORS OF PLEURA: A LIGHT AND ELECTRON MICROSCOPIC STUDY. (E.) Hernandez, F. J. (Lutheran Hosp., Park Ridge, Ill.) and B. B. Fernandez. *Cancer* 34(5):1667-1674, 1974.
- 2821 LYMPHOMATOID GRANULOMATOSIS OF THE SKIN: LIGHT MICROSCOPIC AND ULTRASTRUCTURAL STUDIES. (E.) Kay, S. (Med. Coll. Virginia, Richmond), Y. S. Fu, N. Minars and J. W. Brady. *Cancer* 34(5):1675-1682, 1974.
- 2822 ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA IN THE SKIN. (E.) Castro, C. (Mayo Clin. Fdn., Rochester, Minn.) and R. K. Winkelmann. *Cancer* 34(5):1696-1705, 1974.
- 2823 STUDIES ON THE CELLULAR TRANSFORMATION IN CARCINOGENESIS. (E.) Sugar, J. (Res. Inst. Oncopathol., Budapest, Hungary) and O. Csuka. *Arch Geschwulstforsch* 43(2):130-136, 1974.
- 2824 CONCURRENCE OF CAROTID BODY TUMOR AND PHEOCHROMOCYTOMA. (E.) Sato, T. (Tohoku U. Sch. Med., Sendai, Japan), H. Saito, K. Yoshinaga, Y. Shibota and N. Sasano. *Cancer* 34(5):1787-1795, 1974.
- 2825 ADAMANTINOMAS OF LONG BONES. (E.) Unni, K. K. (Mayo Clin. Fdn., Rochester, Minn.), D. C. Dahlin, J. W. Beabout and J. C. Ivins. *Cancer* 34(5):1796-1805, 1974.
- 2826 CARCINOMA OF THE VAGINA FOLLOWING CERVICAL CANCER. (E.) Kanbour, A. I. (U. Pittsburgh Sch. Med., Pa.), B. Klionsky and A. I. Murphy. *Cancer* 34(5):1838-1841, 1974.
- 2827 MEDIASTINAL TUMOR OF THYMIC ORIGIN AND RELATED TO CARCINOID TUMOR. (E.) Tanaka, T. (Okayama U. Med. Sch., Japan), S. Tanaka, H. Kimura and J. Ito. *Acta Pathol Jap* 24(3):413-426, 1974.

2828 ANGIOFOLLICULAR LYMPH NODE HYPERPLASIA.
 (E.) Mateja, F. (2nd Dept. Med., Charles
U., Prague, Czechoslovakia), Z. Nozicka, V. Kren
and J. Mazak. *Neoplasma* 21(3):343-349, 1974.

2829 PATHOLOGY OF CARCINOMA OF THE HARD PALATE.
 (E.) Reddy, C. R. R. M. (Andhra Med.
Coll., Visakhapatnam, India), K. Rajakumari and V. R.
Kameswari. *Pathol Microbiol* 41(2):118-124, 1974.

2830 SMALL CELL DYSPLASIA AND *IN-SITU* CARCINOMA
 OF THE MAMMARY DUCTS AND LOBULES. (E.)
Toker, C. (Mount Sinai Sch. Med., City U. New York,
N.Y.). *J Pathol* 114(1):47-52, 1974.

2831 THE ULTRASTRUCTURE OF MALIGNANT SYNOVIOMA.
 (E.) Klein, W. (Dept. Pathol., U. Dussel-
dorf, Germany) and F. Hurth. *Beitr Pathol* 153(2):
194-202, 1974.

See also:

- * (Rev): 2406, 2414, 2428
- * (Chem): 2453, 2521, 2531
- * (Viral): 2600, 2656
- * (Epid-Biom): 2852

- 2832 FAMILY STUDIES IN HODGKIN'S DISEASE. (E.) Fraumeni, J. F., Jr. (Natl. Cancer Inst., Bethesda, Md.). *Cancer Res* 34(5):1164-1165, 1974.

Surveys of Hodgkin's disease have indicated an approximately threefold excess risk in first-degree relatives. It is not yet clear whether the tendency to familial concentration in Hodgkin's disease is due to environment, heredity, or both. An environmental influence is suggested by the fact that in familial Hodgkin's disease, the times of clinical onset for cases in a family have resembled one another more closely than have the ages at onset. Although environmental factors have been implicated in the development of Hodgkin's disease in husband and wife, the instances of connubial disease probably do not exceed expectation. The relatively low level of familial aggregation does not support the view that the disease results from person-to-person transmission of an infectious agent. A genetically determined disorder of immunological response with various manifestations may also be indicated; a genetic disorder of T-cells is potentially indicated. Evidence for genetic mechanisms is also provided by reports of familial Hodgkin's disease among the Amish, an inbred population. It is likely that both genetic and environmental factors are of critical importance and that they may be delineated by laboratory studies of high-risk families.

- 2833 OCCURRENCE OF ORAL AND PHARYNGEAL CANCERS IN TEXTILE WORKERS. (E.) Moss, E. (Dept. Occup. Hlth., U. Manchester, England) and W. R. Lee. *Br J Ind Med* 31:224-232, 1974.

The occupations of male textile workers who died of oral and pharyngeal cancers in the years 1959-1963 were examined to discover whether the high incidence of oral cancer in these workers is associated with particular textile occupations or fibers. There was a 77% excess of deaths from these cancers in male textile workers as a whole compared with the male population of England and Wales, the excess being significant at the 0.1% level. An excess occurred in each of the three sites, tongue, mouth, and pharynx, and is significant at the 5% level in the first two sites but not in the third. Fiber preparers had an excess of 330%. Fiber preparing is one of the dustiest occupations in the textile industry and there may well be an association between the inhalation of dust by textile workers and oral and pharyngeal cancers. Weavers and knitters had a deficit of 32% and the remaining three groups, spinners, bleachers, and miscellaneous, had moderate excesses of from 32 to 85%, none of the four being statistically significant.

- 2834 TIME-SPACE CLUSTERING AMONG CASES OF BURKITT'S TUMOR. (E.) Brown, T. M., Jr. (USPHS Ctr. Disease Control, Cancer Birth Defects Div., Atlanta, Ga.) and C. W. Heath, Jr. *Cancer Res* 34(5):1216-1218, 1974.

Time-space clustering has been described as a particular feature of Burkitt's tumor (BT) in Africa, the evidence resting largely on 1967 data from the

West Nile District of Uganda. The results suggest a general drift in case occurrence over time from one geographic region to another. However, no evidence of clustering among cases of BT at any time or space interval has been found in the region surrounding Kampala or the East and West Mengo districts of Uganda, and other data suggesting that cases of BT in Africa may come in clusters consist of purely anecdotal accounts of individual clusters. While there is no general indication that BT tends to be familial, at least four multiple-case family situations have been described, three in Africa and one in the United States. Two other nonfamilial clusters have also been described in the United States. The question of time-space clustering in relation to BT needs further attention. If clustering exists, it may be detectable on a fixed-distance scale only when densely and sparsely populated areas are examined separately. In addition, while the present absence of epidemiological associations other than time-space closeness among cases in individual clusters does not preclude interpersonal spread of infection, discovery of their presence would support the idea that such time-space clustering is more than a chance affair.

- 2835 CANCER RESISTANCE: PART II. (E.) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.) and H. A. Guirgis. *Nebr Med J* 59(6):192-196, 1974.

The familial incidence of cancer of all anatomic sites was studied in the families of 4,270 consecutive persons undergoing routine cancer screening examinations or participating in a breast-milk study. Approximately 46% of the families were cancer free, and only 7% were predominantly cancer prone. The ratio of families with a single member with breast cancer to those with a multiple incidence of breast cancer was 11.8 to 1.0. Only 0.7% of the families had more than one member with breast cancer, while 7.4-9.1% had one member with breast cancer. The data demonstrate marked variability in the distribution of cancer among families of normal individuals from the general population. They support the view that genetic differences play prominent roles in a family's cancer proneness and its cancer resistance, but they do not exclude the role of nongenetic factors. The data also show that certain types of cancer are particularly liable to develop in genetically predisposed individuals.

- 2836 MORTALITY STUDY OF WORKERS IN THE MANUFACTURE OF VINYL CHLORIDE AND ITS POLYMERS. (E.) Tabershaw, I. R. (Tabershaw-Cooper Assoc., Inc., Rockville, Md.) and W. R. Gaffey. *J Occup Med* 16(8):509-518, 1974.

This study of 8384 men who had a least one yr of occupational exposure to vinyl chloride before December 31, 1972, demonstrates that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The

mortality from other cancers was lower than that of the general male population with the exception of cancer of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. No explanation has been found for the latter finding. The other major findings of the study are: 1) the overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; 2) no cause of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and 3) no deaths identified as angiosarcoma of the liver were found other than those previously identified. This is the first epidemiological study suggesting that vinyl chloride may also be associated with human cancer of multiple sites.

2837 THE EPIDEMIOLOGY OF CANCER OF THE BUCCAL CAVITY AND PHARYNX IN OKLAHOMA. (E.)

Booze, C. F. (U. Oklahoma Hlth. Sci. Ctr.) and N. R. Asal. *J Okla State Med Assoc* 67(8):367-372, 1974.

Mortality data for cancer of the buccal cavity and pharynx among Oklahoma residents during the period 1950-1970 were analyzed for age, sex, race, geographic, and secular trends. Generally, findings for the Oklahoma data paralleled previously recognized trends with regard to the epidemiologic variables under consideration. Limited data for Oklahoma Indians are suggestive of somewhat decreased mortality from this cause; however, small numbers preclude definitive statements. While consistent with urban-rural expectations, unusual clustering of excess mortality in certain geographic areas of the state are suggestive of a common etiology.

2838 MULTIPLE PRIMARY NEOPLASMS IN BLACKS COMPARED TO WHITES. III. INITIAL CANCERS OF THE FEMALE BREAST AND UTERUS. (E.) Newell, G. R. (Tulane Med. Ctr., New Orleans, La.), W. Rawlings, E. T. Kremenz and J. D. Roberts. *J Natl Cancer Inst* 53(2):369-373, 1974.

The incidence of second primary cancers among white and black women with initial cancers of the breast, cervix, and corpus uteri was determined from the experience of the Charity Hospital of Louisiana Tumor Registry. Observed second primary cancers were compared with expected numbers to obtain a direct estimate of risk. Both white and black females with initial breast cancer had an excess risk of developing cancers of the buccal cavity and pharynx and an additional breast cancer. White females with breast cancer had a slightly increased risk for developing cancer of the lung and ovary and black females for developing cancer of the corpus uteri and leukemia. Both white and black women with initial cancer of the cervix had a excess risk for subsequent cancers of the buccal cavity and pharynx and lung. Women with cervical cancer had a small increased risk for subsequent bladder cancer. The limitations and advantages of this type of study are discussed.

2839 THE PREDICTION OF CANCER INCIDENCE IN FINLAND FOR THE YEAR 1980 BY MEANS OF CANCER REGISTRY MATERIAL. (E.) Teppo, L. (Finnish Cancer Registry, Helsinki), T. Hakulinen and E. Saxen. *Ann Clin Res* 6(2):122-125, 1974.

The data of the Finnish Cancer Registry for 1957-1968 were applied to predict the incidence rates of different types of cancer, and the number of new cancer patients in Finland in 1980. From these data, indications are that the total incidence will remain unchanged. It is expected that an increase will occur in the incidence of cancer of the lung (males), colon, rectum, pancreas, prostate, urinary organs, skin, and also in that of Hodgkin's disease, lymphoma and multiple myeloma. A decreasing trend is predicted for cancer of the stomach, esophagus, mouth, pharynx and lip. In 1980, lung cancer will be the commonest type of cancer in males (35%) and that in females cancer of the breast (20%) will predominate. It is noted, however, that changes in social habits and of mass-screening programs for early cancer detection may invalidate some of the estimates.

2840 PROPORTIONAL MORTALITY AMONG VINYL-CHLORIDE WORKERS. (E.) Monson, R. R. (Harvard Sch. Pub. Hlth., Boston, Mass.), J. M. Peters and M. N. Johnson. *Lancet* II(7877):397-398, 1974.

In a proportional-mortality analysis of 161 deceased workers in two plants using vinyl chloride, a 50% excess of deaths due to all cancer was seen. Specific sites of cancer with the greatest excess included liver and biliary tract, lung, and brain. The excess in fatal cancer was seen mainly in men who died before age 60. Also, there was a trend in time in the ratio of observed to expected deaths: since 1970 the expectancy of deaths from cancer has more than doubled.

2841 CANCER OF THE ALIMENTARY TRACT IN COSTA RICA. (E.) de Madrigal, L. M. (Ministry Pub. Hlth., San Jose, Costa Rica). *Paho Bull.* 9(2):150-164, 1974.

Costa Rican death and hospital discharge statistics relating to cancer of the alimentary tract were analyzed for the period 1956-1969. When the mortality rates for Costa Rica are compared with those for 24 other countries, it is seen that Costa Rica's death rates are moderate for cancer of the esophagus, very low for cancer of the large intestine, and very high for cancer of the stomach. Of the countries studied, Costa Rica was among the three countries with the highest stomach cancer mortality rates, having a rate similar to those found in Chile and Japan, which were also very high. A progressive increase is seen over the 14 yr studied with respect to cancer of the esophagus in both males and females, but there was also a marked reduction in the ratio of male:female discharges and deaths during this period. Cancer of the alimentary tract was more frequent in the central part of the country than in the coastal regions. Factors having a significant impact on the occurrence of cancer are discussed.

- 2842 RESPIRATORY CANCER AMONG CHROMATE WORKERS.
(E.) Enterline, P. E. (U. Pittsburgh, Pa.).
J Occup Med 16(8):523-526, 1974.

This is a review of prospective epidemiological investigations of workers engaged in the refining of chromite ore. The earliest such study covered the period 1930 to 1947 and included workers in chromate plants in the U.S. It showed a relative risk of dying from respiratory cancer 20 times the rate for a control population. A later study of these plants for the period 1940 to 1948 showed a relative risk for respiratory cancer of 29, ranging from a 40-fold risk for persons in the age group 15 to 44 to a 20-fold risk at ages 55 to 74. The most recent study of American chromate workers was for the period 1937 to 1960 and confirmed the high respiratory cancer death rates observed in earlier studies and the age relationship. It also showed, however, that the risk was highest shortly after the cohort was identified as being actively employed in the chromate industry, suggesting a short latent period probably as a result of exposure to a very potent carcinogen. Recent animal experiments suggest that the carcinogenic agent in the old chromate producing plants was calcium chromate; further epidemiological studies are needed for verification of this observation.

- 2843 VAGINAL AND CERVICAL ABNORMALITIES, INCLUDING CLEAR-CELL ADENOCARCINOMA, RELATED TO PRENATAL EXPOSURE TO STILBESTROL. (E.) Scully, R. E. (Harvard Med. Sch., Boston, Mass.), S. J. Robboy, and A. L. Herbst. *Ann Clin Lab Sci* 4(4): 222-233, 1974.

A variety of vaginal cervical abnormalities have been seen in the offspring of women who took stilbestrol or chemically related nonsteroidal estrogens during pregnancy. Cervical erosion has been the most noted abnormality, but vaginal adenosis has been proven by biopsy in over 30% of the offspring studied, and transverse vaginal and cervical ridges have been seen in approximately 10% of the exposed population. In addition, a total of 170 cases of clear-cell adenocarcinomas of the vagina and cervix have been reported in the world literature. These latter tumors have been characteristically superficial and either polypoid, papillary, or nodular, ranging in diameter from less than 1 to over 10 cm. Malignant cells have been found in most of the cases reviewed, and distant metastases have been encountered significantly more frequently than in reported series of squamous cell carcinomas of the cervix and vagina. Vaginal adenosis is usually accompanied by an inflammatory reaction as well as alterations in the associated squamous epithelium. No clearcut transitions between the adenosis and the carcinomas have been revealed. Although the role which stilbestrol and related drugs play in the development of such abnormalities has not been elucidated, alterations in the development of the lower genital tract appear to be produced during the first 4 months of pregnancy. Estrogens of ovarian origin may play a possible pathogenic role. It is likely that the clear-cell adenocarcinomas of

the cervix and vagina are of mullerian origin. It is important that cytologists and pathologists become familiar with the various abnormalities associated with stilbestrol and related drug use so that additional epidemiologic, clinical, and pathological information can be acquired.

- 2844 OIL AND CANCER. (E.) Kipling, M. D. (Employment Med. Advisory Serv., Birmingham, England). *Ann R Coll Surg Engl* 55(2): 71-79, 1974.

Several epidemiological studies have shown a relatively high incidence of skin cancers, especially scrotal, due to occupational exposure to mineral oil in shale oil workers, cotton mule spinners and machine operators in the Birmingham, England region. Comparison of work conditions in two Birmingham shops, one with a high incidence and the other with no incidence of scrotal cancer among workers, showed no essential differences in equipment or exposure. The type of work, however, was of importance, with the greatest risk occurring in tool setters, setter operators, sheet metal rollers, tube drawers, drop forgers, brick and tile moulders, and metal hardeners, all types of work in which there was close contact with oil. The age of incidence varied from 27 to 71 yr with an average age of 58. The greater the age at first exposure, the shorter the exposure time required for development of scrotal cancer. Exposure to oil mists may also place workers at risk for cancers of the respiratory tract and other organs exposed to oil. Experimental evidence indicates that mixtures of polycyclic aromatic hydrocarbons are probably the carcinogenic elements in oils. Preventive measures for oil cancers are cited.

- 2845 FURTHER OBSERVATIONS ON CANCER IN A STEEL CITY. (E.) Cecilioni, V. A. (Hamilton Gen. Hosp., Ontario, Canada). *Fluoride* 7(3):153-165, 1974.

The relationship between atmospheric pollution, mortality from cancer, respiratory diseases, and hospital admissions was studied in Hamilton, Ontario between the years 1969 and 1970. Cancer of the trachea, bronchus, and lungs accounted for 225 deaths in Hamilton during this period. Between 1966 and 1970, the incidence of cancer of the larynx, trachea, bronchus, lung, stomach, bladder, and prostate was about 1/3 higher in Hamilton than in the less industrialized city of Ottawa. The highest mortality rate from cancer (65/100,000) occurred in the proximity of Hamilton's steel mills, compared with the death rates (23 and 12 per 100,000) farther distant. Admission records at two large Hamilton hospitals showed a close correlation between respiratory disease and the daily pollution index. The high atmospheric concentrations of fluoride, a major pollutant derived from the manufacture of steel, appear to be related to the high death rates from cancer of the respiratory, gastrointestinal, and genito-urinary systems in Hamilton. These environmental effects appear to be more important in this respect than cigarette smoking.

- 2846 FAMILIAL CANCER OF THE ESOPHAGUS IN IRAN. (E.) Pour, P. (U. Nebraska Med. Ctr., Omaha) and P. Ghadirian. *Cancer* 33(6):1649-1652, 1974.

A retrospective case-control interview study followed by medical examinations uncovered 14 cases of esophageal cancer among the 63 inhabitants (representing 12 families) of Sabsevar, a small village in north-eastern Iran. Thirteen of the esophageal cancer patients were descended from the same parents, and all members of the fourth and fifth generations of this family suffered from the disease. The lifespan of the descendants with esophageal cancer was shorter in the fourth and much shorter in the fifth generations, compared with other esophageal cancer patients in other high-incidence areas of northeastern Iran, indicating an earlier onset of the carcinoma in each generation. Five of the patients were miners, four were farmers, and four were housewives who wove carpets part of the time. The aggregation of cancer in this family may reflect an environmental influence on genetically susceptible individuals and suggests inheritance as a possible oncogenic factor.

- 2847 MORPHOMETRIC ANALYSIS OF SARCOMAS WITH DIFFERENT KARYOTYPES. (E.) Lindberg, L. G. (Inst. Path., U. Lund, Sweden) and F. Mitelman. *Lab Invest* 31(1):90-95, 1974.

Rous virus-induced sarcomas with a polyploid karyotype were analyzed using morphometric methods. The results are compared with previous findings in diploid and aneuploid sarcomas and, in addition, related to a similar morphometric analysis of chemically (7,12-dimethylbenz(a)anthracene)-induced sarcomas with both a normal diploid and a polyploid karyotype. The results indicate that the cellular morphology is altered in a nonrandom and possibly predetermined way and is related to the predetermined sequence of chromosomal changes when a malignant tumor undergoes an evolution from a normal karyotype to an abnormal karyotype. Some cell constituents are unaffected by the chromosomal evolution from diploidy to polyploidy. In addition, there are no striking differences, as regards these unaffected parameters, between tumor cells induced by the two widely different carcinogens. This might indicate that there is a limited range in the host cell within which some constituents of a cell may vary; if these boundaries are trespassed a reproductive cell cycle can not be maintained and the cell line is eliminated from a progressively changing tumor.

- 2848 FAMILIAL MEDULLARY THYROID CARCINOMA AND PHEOCHROMOCYTOMA: EPIDEMIOLOGIC INVESTIGATIONS. (E.) Fredrick, P. L. (Nat'l. Cancer Inst., Bethesda, Md.), K. E. W. Melvin, A. H. Tashjian, Jr., P. H. Levine and J. F. Fraumeni, Jr. *J Nat'l Cancer Inst* 52(1):285-287, 1974.

Epidemiologic studies were made of familial medullary thyroid carcinoma-pheochromocytoma (MCT) syndrome occurring in an autosomal dominant pattern in 20 members of a kindred, including 13 with occult tumors

diagnosed by laboratory surveillance. Parathyroid hyperfunction, neurocutaneous lesions, dermatoglyphic aberrations, serologic hyperreactivity to Epstein-Barr virus, and increased in vitro viral transformation of skin fibroblasts were detected in some family members. This study suggests clues to identify family members at high risk of MCT. The familial MCT indicated a pattern of involvement consistent with autosomal dominant inheritance. The etiologic and prognostic significance may be clarified by careful follow-up and evaluation of the kindred for new tumors.

- 2849 HEPATIC DISEASE AMONG WORKERS AT A VINYL CHLORIDE POLYMERIZATION PLANT. (E.) Falk, H. (Ctr. Dis. Control, Atlanta, Ga.), J. L. Creech, Jr., C. W. Heath, Jr., M. N. Johnson and M. M. Key. *JAMA* 230(1):59-63, 1974.

Eleven cases of hepatic disease, including seven cases of hepatic angiosarcoma, have been identified to date among men employed at one vinyl chloride polymerization plant in Louisville. The earliest diagnosis was made in April 1964. The two most recent cases, both angiosarcoma, were diagnosed in February 1974 as a result of systematic medical screening for liver abnormalities among workers at the plant. Ages at diagnosis have ranged from 36 to 58 yr for the seven patients with angiosarcoma and from 28 to 56 yr for the four patients with nonmalignant disease; durations of employment before diagnosis have ranged from 12 to 28 yr (average 18.0) and from 5 to 29 yr (average 20.6). All 11 persons had worked in close and continuous contact with various phases of the vinyl chloride polymerization process. Review of pathologic material suggests the presence in both tumor and nontumor cases of portal fibrosis and atypical sinusoidal lining cells. A direct causal relationship between exposure to vinyl chloride monomer and pathologic findings is postulated.

- 2850 INADEQUATE CORPUS LUTEUM FUNCTION: A PATHOPHYSIOLOGICAL INTERPRETATION OF HUMAN BREAST CANCER EPIDEMIOLOGY. (E.) Sherman, B. M. (U. Iowa Hosp., Iowa City) and S. G. Korenman. *Cancer* 33(5):1306-1312, 1974.

Detailed hormonal studies of normal and abnormal human reproductive cycles have led to the conclusion that inadequate corpus luteum secretory function is one of the characteristic features of infertile and/or irregular menstrual cycles. In states of altered ovarian function, the breast is probably subject to the consequences of disordered secretion of both ovarian and pituitary hormones. The risk of breast cancer is increased with late first pregnancy, nulliparity, early menarche, late menopause, obesity, low androgen secretion, and a decreased excretion of estradiol relative to the excretion of estrone and estradiol. The risk is decreased with early first pregnancy and castration. Oral contraceptives and lactation have no apparent effect. The frequent occurrence of menstrual cycles deficient in progesterone secretion may be the physiological basis for these risk factors: estrogenic stimulation in the absence of sufficient cyclic progesterone secretion may provide

a setting favorable to the development of mammary carcinoma. If this hypothesis is substantiated in epidemiologic studies, a vigorous attempt can be made early in reproductive life to identify and treat those who manifest luteal phase inadequacy.

2851 POST-MORTEM INVESTIGATION OF OCCULT THYROID CARCINOMA IN ENDEMIC GOITER REGIONS.

(Ger.) Balazs, Gy. (Med. Univ. Debrecen, Hungary) and G. Krasznai. *Wein Klin Wochenschr* 86(12):339-344, 1974.

Postmortem investigations of 200 patients who died from diseases other than those of the thyroid gland or cancer in an endemic goiter region in Ungarn were carried out to determine the incidence and histomorphology of occult thyroid carcinoma in symptom-free patients. Nine tumors were detected by means of serial histological sections, 8 of which were differentiated and 1 undifferentiated. Two carcinomas had metastasized into the regional lymph nodes. Two papillary carcinomas were found. Two carcinomas were of microscopic size, one measuring 1.5 cm, while the rest ranged from 3 to 8 mm. Three carcinomas were found in inflamed thyroid tissue, and advanced, destructive Hashimoto thyroiditis was detected in 2 cases. According to the present investigation, thyroid carcinoma is not a rare tumor in this region, and a causal relationship between nodular goiter and carcinoma of the thyroid gland is suggested. Iodine prophylaxis in endemic goiter regions results in pronounced differentiation of the structure and improved prognosis of carcinoma of the thyroid gland.

2852 MODES OF GROWTH AND SPREAD OF A TRANSPLANTABLE, VIRUS-PRODUCING MURINE (MOLONEY) SARCOMA: KARYOTYPIC ANALYSES. (E.) Russell, S. W.

(Dept. Exp. Pathol., Scripps Clin. Res. Found., La Jolla, Calif.), U. Francke, L. Buettner and C. G. Cochrane. *J Natl Cancer Inst* 53(3):801-806, 1974.

This study was designed to show how Moloney sarcoma virus produced *in vivo* by tumor cells may affect the development of primary and secondary Moloney sarcomas. Cloned cells of a virus-producing, transplantable murine (Moloney) sarcoma line (MSC) contained a set of stable, structurally rearranged, "marker" chromosomes. These identifying markers were not present in cells newly transformed by murine sarcoma virus (MSV). It was therefore possible, after MSC cell injection, to determine whether or not any causal relationship existed between MSV produced *in vivo* and subsequently developing primary and secondary neoplasms. Each adult and neonatal BALB/c strain mouse given 10^6 MSC cells developed a progressing primary sarcoma. Many exhibited secondary pulmonary neoplasms as well, and some neonates developed secondary tumors in their spleens and periosteal tissues. Of 879 metaphase spreads prepared from primary and pulmonary neoplasms, all contained MSC marker chromosomes. In contrast, cells explanted from a periosteal tumor of a neonatal mouse uniformly lacked such markers, even though the primary sarcoma of the

same mouse consisted of MSC cells exclusively. Similarly, none of 180 metaphase spreads obtained from sarcoma virus-induced primary tumors contained MSC marker chromosomes. Primary sarcomas and secondary pulmonary neoplasms--the lesions most frequently encountered in this system--developed, respectively, by replication and metastasis of MSC cells. Virus recruitment of new tumor cells appeared to have only a minor role associated with the spread of sarcomas in neonatal mice.

2853 QUANTITATION OF TOTAL-BODY TUMOR CELLS (MOPC 104E). I. SUBCUTANEOUS TUMOR MODEL.

(E.) Ghanta, V. K. (U. Alabama Med. Ctr., Birmingham) and R. N. Hiramoto. *J Natl Cancer Inst* 52(4):1199-1202, 1974.

Tumor IgM was estimated in 15 mice with 1, 2, and 4 sites of s.c. implanted tumor to quantitate the *in vivo* cellular immunosynthetic functions and the number of tumor cells in each mouse. There was a good correlation between tumor size, tumor cell number calculated by IgM measurements, and the estimated tumor cells based on tumor wt. The equations for the mathematical model used to estimate total number of tumor cells is given. The various parameters for the model had been previously determined. A direct quantitative relationship was confirmed between the number of tumor cells in a solid implant and the computer-generated tumor cell numbers based on experimentally measured parameters of the tumor population and the tumor product. The animal model as developed for solid myeloma implants can be applied to the study of chemotherapeutic effects of tumor-inhibiting agents and can also serve as a means for continual monitoring of the tumor load in individual animals.

2854 BREAST CANCER IN PREMENOPAUSAL AND POSTMENOPAUSAL WOMEN. (E.) Stavsky, K.

(Ontario Cancer Treatment Res. Fdn., London, Canada) and S. Emmons. *J Natl Cancer Inst* 53(3):647-654, 1974.

A case-control study was done to determine if the risk factors for breast cancer differed between premenopausal and postmenopausal women. The subjects included 95 premenopausal and 278 postmenopausal women with breast cancer admitted to the Ontario Cancer Foundation Clinic, London, Canada between June 1967 and February 1971. Controls were 106 premenopausal and 480 postmenopausal women with benign and malignant disease of sites other than breast, admitted to the same clinic during the same period. Breast cancer risk increased with increasing age at first pregnancy among postmenopausal women only. Among the premenopausal women, increased breast cancer was associated with early menarche. Late age at natural menopause was an important risk factor for postmenopausal women; the risk in women experiencing natural menopause over the age of 55 was 2.5 times as great as that of women undergoing menopause before age 40. A longer interval between age of menarche and age at first pregnancy increased the risk in both groups. Use of oral contraceptives, or duration of use, did not

increase the risk of breast cancer. Among oral contraceptive users, there was a trend toward greater risk with increasing age at first use of oral contraceptives.

- 2855 AN EPIDEMIOLOGIC APPROACH TO CANCER OF THE LARGE INTESTINE: THE SIGNIFICANCE OF DISEASE RELATIONSHIPS. (E.) Burkitt, D. P. (Med. Res. Council, London, England). *Dis Colon Rectum* 17(4): 456-461, 1974.

Epidemiologic associations between two or more diseases can be used as signposts which may point towards possible common causative factors. Adenomatous polyps, diverticular disease, appendicitis, hiatal hernia, and colon cancer are closely associated epidemiologically and, in some cases, in individual patients. Cancer and adenomatous polyps of the large bowel may result, at least in part, from the same causes - "enhanced carcinogenesis". Hiatal hernia is caused by increased abdominal pressure, and diverticular disease appears to be caused by increased intraluminal pressures. Increased intraluminal pressures, increased intra-abdominal pressures, and enhanced carcinogenesis are closely associated with each other. Fecal arrest is believed to be the major cause of both increased intraluminal pressures and increased intra-abdominal pressures; fecal arrest, in turn, most frequently results from a diet deficient in plant fiber content. Enhanced carcinogenesis may also be linked, through fecal arrest, to a fiber-depleted diet. Thus, return to a high-residue diet should, in time, result in a reduced frequency of these diseases; there is no evidence that such an increase would result in any conceivable harm. Since an increased incidence of appendicitis has been observed epidemiologically to precede an increased incidence of any of these diseases, higher incidence rates of these diseases may follow increased incidence rates of appendicitis if the dietary changes associated with the latter are continued and increased.

- 2856 SECULAR TRENDS IN LEUKEMIA MORTALITY. (E.) Infante, P. F. (Ohio Dept. Hlth., Columbus), J. H. Ackerman and A. L. MacKenzie. *Lancet* (7882): 720-721, 1974.

Age-specific mortality rates by sex for four conservative 5-yr periods covering the yr, 1953-72 were analyzed using data from Ohio death certificates. Data for combined sexes aged 0-19 yr showed a declining death rate through 1968-72, with the greatest rates of decline being for the periods 1958-62 and 1963-67. The age distribution for 1963-67, compared with the periods 1953-57 and 1958-62, suggested that the reduction in mortality rates in 1963-67 were primarily the result of a decreased incidence of leukemia in the 1-4 yr-old group. During the final two periods, 1963-67 and 1968-72, the mode of distribution shifted from the 1-4 yr-old group to the 5-9 yr-old group, suggesting a postponement in leukemia mortality possibly secondary to more effective cancer chemotherapy. The data indicated that the overall incidence of leukemia is leveling off. Analysis of death rates of

children with acute lymphocytic leukemia for the period 1968-72 showed a peak incidence for the 5-9 yr-old group, a finding also consistent with an increased life span in these patients. It is suggested that the shift in the peak of mortality-rate of acute lymphocytic leukemia to a later age may be the result of lag in mortality.

- 2857 FAMILIAL CANCER PREVALENCE SPANNING EIGHT YEARS. (E.) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.). *Arch Intern Med* 134(5):931-938, 1974.

Family N, which showed an extraordinarily high frequency of adenocarcinoma in specific branches of the family, consistent with the cancer family syndrome, was extensively investigated. During an 8-yr period, cancer was found to have occurred in 21 additional family members. Six of the individuals in whom cancer had been previously ascertained 28% of those who developed cancer during this eight-year period, were found to have acquired additional primary cancers. One of them had four separate primary cancers, and another one had three. Pedigree analyses have shown repeatedly that individuals from particular lineages tend to develop cancers of specific anatomic sites. It is suggested that gene-transmitted constitutional differences may interact with non-genetic factors, possibly oncogenic viruses, to produce cancer in such family members who are at relatively high risk. Cancer control programs utilizing established familial risk information should be developed for better management of these familial cancer problems.

- 2858 EXPONENTIAL GROWTH. (E.) Bjerknes, R. (Inst. Physics, U. Oslo, Norway). *Eur J Cancer* 10(3):165-168, 1974.

A Burkitt tumor may be assumed to be an exponentially expanding cell population in which a constant percentage of the proliferative cells enters the DNA-synthesis phase per time unit; it is also assumed that there is only one cell type present. Based on these assumptions, the results of biological experiments were used to develop a mathematical tumor model incorporating numerical values of different relevant cell parameters. Assuming a constant growth rate, the following formula was derived: $R \cdot T_d = \ln 2 / (1 - \lambda)$, where R is the rate of proliferation, T_d is the actual clinical doubling time, and, in the case of zero cell loss, $\lambda = 0$. This formula is inadequate in cases with large cell loss however. For cases with large loss, the following formula would be usable for practical applications: $R \cdot T_d = 0.02 / (1 - \lambda)$, where R is measured per hour and T_d is measured in days. The following formula is approximately valid for an exponentially growing population: $LI = R_s \cdot T_s$, where LI is the labeling index, R_s is the rate of cells entering the DNA-synthesis phase or S-phase, and T_s is the mean time spent in S-phase. The numerical results from a previous paper dealing with the cell kinetics of a Burkitt tumor were analyzed and a combined loss factor of 69% of the total expected increase in cell number was found.

2859 THE INTERRELATIONSHIP OF COITUS AND VAGINAL BACTERIAL FLORA IN THE GENESIS OF CANCER OF THE UTERINE CERVIX. (E.) Leppaluoto, P. (Lab. Cancer Soc., Tampere, Finland). *Cancer Cytol* 14(1):6-8, 1974.

2860 FAMILIAL HODGKIN'S DISEASE. (E.) Fennelly, J. J. (Our Lady's Hosp., Dublin, Ireland) and A. MacBride. *Br J Cancer* 29(1):98-99, 1974.

2861 INCIDENCE OF CARCINOMA OF STOMACH AND TUMOUR TYPE. (E.) Whitehead, R. (Radcliffe Infirm., Oxford, England), J. M. Skinner and P. J. Heenan. *Br J Cancer* 30(4):370-372, 1974.

2862 GASTRIC CARCINOMA IN YOUNG PATIENTS. (Ger.) Moritz, E. (Surg. U. Clin., Vienna, Austria) and G. Wense. *Dtsch Med Wochenschr* 99(5):180-181, 1974.

2863 FAMILIAL POLYPOSIS OF COLON AND RECTUM. (Ger.) Hantschmann, N. (Surg. U. Clin., Kiel, Germany) and B. Nemsman. *Dtsch Med Wochenschr* 99(10):453-457, 1974.

2864 EVIDENCE OF CLUSTERING IN CASES OF GASTRO-INTESTINAL TRACT MALIGNANCY. (E.) Bedwani, R. (Regional Cancer Registry, Birmingham, England), C. R. Gillis and J. A. H. Waterhouse. *Br J Cancer* 29(1):100, 1974.

2865 MORTALITY FROM MALIGNANT DISEASE IN PATIENTS WITH ASTHMA. (E.) Alderson, M. (Wessex Regional Hlth. Authority, Winchester, England). *Lancet* II(7895):1475-1477, 1974.

2866 EPIDEMIOLOGICAL ANALYSIS OF THE MOST PRE-VALENT SITES AND TYPES OF CANINE NEOPLASIA OBSERVED IN A VETERINARY HOSPITAL. (E.) Cohen, D. (Sch. Vet. Med., U. Pennsylvania, Philadelphia), J. S. Reif, R. S. Brodey and H. Keiser. *Cancer Res* 34(11):2859-2868, 1974.

See also:

- * (Rev): 2404, 2409, 2423, 2424, 2438
- * (Chem): 2529, 2531

- 2867 CANCER IN THE MALE BREAST. (E.) Panettiere, F. J. (U. Texas Med. Branch, Galveston). *Cancer* 34(4):1324-1327, 1974.

From 1957 to 1972, 17 cases of breast cancer in men (16 carcinomas and 1 liposarcoma) were diagnosed at U.S. Air Force hospitals. The median age at onset was 48 yr, with a range of 25-62 yr. The median delay to treatment was 3 months, which may explain the relatively high 5-yr survival rate of 65.6%. However, only 1 of 8 patients first treated 4-72 months after the first symptoms of breast cancer has had any recurrence. These data disprove the belief that men with breast cancer have a poorer prognosis than women with breast cancer, and that the outcome is aggravated by a prolonged delay before therapy is instituted. Analysis of these 17 cases and 311 others reported in the literature showed 26 patients (7.9%) with a least one additional primary tumor in an organ other than skin. This pattern of additional primary tumors in men is similar to that reported for women with breast cancer.

- 2868 SUPPRESSION OF FIBRINOLYSIN T ACTIVITY FAILS TO RESTORE DENSITY-DEPENDENT GROWTH INHIBITION TO SV3T3 CELLS. (E.) Chou, I.-N. (Massachusetts Gen. Hosp., Boston), P. H. Black and R. O. Roblin. *Nature* 250(5469):739-741, 1974.

An assay for fibrinolytic activity, that measures cumulative proteolytic hits over a prolonged period and uses ϵ -aminocaproic acid (EACA), an inhibitor of plasminogen activation and fibrinolysin T activity, is described. Medium containing 10 mg/ml EACA was added to Swiss simian virus 40 transformed-3T3 (SV3T3) cells after plating them on ^{125}I -fibrin coated dishes. The effects of EACA on cell growth and release ^{125}I -fibrinopeptides was simultaneously determined. Fibrinolysin T activity in EACA-treated cultures remained low and relatively constant for a least seven days after plating. The results indicate that essentially complete suppression of fibrinolysin T activity failed to restore density-dependent growth inhibition to SV3T3 cells. High levels of fibrinolytic activity were observed in growing cultures of both 3T3 and SV3T3 cells and only when confluent 3T3 cell were compared with growing SV3T3 cells did the SV3T3 cells exhibit higher fibrinolytic activity per 10^6 cells than the 3T3 cell cultures. The enhanced fibrinolysin T activity of SV3T3 cells is unlikely, therefore, to be the cause, but may rather be a consequence of unrestrained cell growth.

- 2869 RECEPTOR MOBILITY AND THE MECHANISM OF CELL-CELL BINDING INDUCED BY CONCAVALIN A. (E.) Rutishouser, U. (Weizmann Inst. Sci., Rehovot, Israel) and L. Sachs. *Proc Natl Acad Sci USA* 71(6):2456-2460, 1974.

The cell-cell binding induced between single cells by concanavalin A (Con A) was analyzed using normal rat and mouse lymphocytes and Moloney virus-induced lymphoma cells attached to nylon fibers. The binding of a Con A-coated cell to an untreated cell was frequently observed with lymphoma tumor cells, less

frequently seen between a lymphoma cell and a normal lymphocyte, and only rarely seen between two lymphocytes. The binding was inhibited by the presence of a saccharide inhibitor of Con A (α -methyl-D-mannopyranoside, α -MM), but could not be reversed by adding α -MM after the cells had already bound to each other. Although no binding was obtained when both cells were coated with lectin or fixed with glutaraldehyde, fixation of a cell before coating with Con A enhanced its ability to bind an untreated cell. The results indicate that the cell-cell binding induced by Con A requires short-range lateral movement of the cell receptors for lectin, that only one cell has to have mobile receptors, and that some receptors must be unoccupied by lectin molecules before cell-cell contact. Clustering of the receptors is not necessary and seems to hinder cell-cell binding. The short-range movement appears to be required for alignment of the individual receptors so as to form multi-point bridges between two cells by lectin molecules. The bridging is then followed by the formation of irreversible bonds between the cells. The receptors on tumor cells appear to have a greater ability than those on normal cells to align themselves for cell-cell binding.

- 2870 CYTOPLASMIC GLUCOCORTICOID-BINDING PROTEINS IN GLUCOCORTICOID-UNRESPONSIVE HUMAN AND MOUSE LEUKEMIC CELL LINES. (E.) Lippman, M. E. (Nat'l. Cancer Inst., Bethesda, Md.), S. Perry and E. B. Thompson. *Cancer Res* 34(7):1572-1576, 1974.

Cytoplasmic glucocorticoid-binding proteins of high affinity and specificity were identified, quantified, and partially characterized in three steroid-unresponsive tissue culture lines, one derived from an AKR mouse leukemia and two derived from human lymphoblastic leukemia cells. The number of receptors/cell appeared to be comparable to that found in many steroid-responsive cells. Temperature-dependent entry of cytoplasmic receptor into the nucleus did not appear to be abnormal as determined in an *in vitro* nuclear binding assay. Cell growth, nucleoside and amino acid incorporation into macromolecules, amino acid pools, and glucose uptake were found to be unaffected by added glucocorticoid. The presence of specific cytoplasmic receptor proteins for glucocorticoids in malignant tissue does not appear to guarantee steroid responsiveness.

- 2871 THE ABSENCE OF A PYRIMIDINE DIMER REPAIR MECHANISM IN MAMMALIAN MITOCHONDRIA. (E.) Clayton, D. A. (Stanford U. Sch. Med. Calif.), J. N. Doda and E. C. Friedberg. *Proc Natl Acad Sci USA* 71(7):2777-2781, 1974.

Experiments were conducted to determine whether mammalian cells can repair UV light-induced pyrimidine dimers in their mitochondrial DNA. The assay system was based upon the ability of the phage T4 UV endonuclease to nick covalently closed circular mitochondrial DNA that contain pyrimidine dimers. The results show that dimers are not removed from the mitochondrial DNA of mouse L cells or human KB and HeLa cells. There is also no evidence for photoreactivation of mitochon-

drial DNA. Analyses of ethidium bromide-caesium chloride equilibrium density gradients of mitochondrial DNA isotopically labeled before and after exposure to UV light show that the total amount of DNA replication is depressed after exposure. In addition, an increase in the frequency of molecules banding at a position expected for intermediate replicating forms and open circular daughter molecules suggests that the rate of replication is slower (or arrested) in molecules with pyrimidine dimers. The absence of a significant amount of mixing of label incorporated before and after UV-irradiation is evidence against the occurrence of a large amount of genetic exchange between mitochondrial DNA molecules under these conditions.

- 2872 TRANSCRIPTION OF NONREPETITIVE DNA IN HUMAN TISSUES. (E.) Sawada, H. (U. Texas System Cancer Ctr., M.D. Anderson Hosp. Tumor Inst., Houston) and G. F. Saunders. *Cancer Res* 34(3):516-520, 1974.

Unique sequences of tritiated DNA prepared from HeLa cells were hybridized with unlabeled RNA extracted from human leukemic, liver, and kidney cells and from cultured human lymphocytes and HeLa cells. The DNA and RNA were not extensively degraded during the long annealing time required for hybridization. The unique DNA-RNA hybrids were thermally stable, indicating that the hybrids contained little mismatching of base pairs. The RNAs from all of the leukemic leukocytes studied (lymphosarcoma, chronic lymphocytic leukemia, acute myelocytic leukemia, and acute lymphocytic leukemia) and from liver and kidney cells had essentially the same saturation value (approximately 2.5%). The results indicated that the amounts of unique genome transcribed in all human leukemic cells are very similar. The fraction of DNA transcribed in cultured normal lymphocytes and HeLa cells was significantly higher than that transcribed in cells from leukemia patients.

- 2873 DNA POLYMERASES IN NORMAL AND LEUKEMIC HUMAN HEMATOPOIETIC CELLS. (E.) Coleman, M. S. (U. Kentucky Med. Ctr., Lexington), J. J. Hutton and F. J. Bollum. *Blood* 44(1):19-32, 1974.

DNA polymerase activities were assayed in bone marrow cells and peripheral leukocytes from normal persons and patients with acute myelogenous, chronic lymphocytic, and chronic myelogenous leukemias. Extracts of subcellular components were fractionated by velocity sedimentation through sucrose density gradients and assayed with activated DNA as template. Two major DNA-dependent DNA polymerases were found in the human cells; they had molecular weights of approximately 50,000 and 200,000 daltons resp. The high-molecular wt DNA polymerase was located in the soluble cytoplasmic fraction and was inhibited by N-ethylmaleimide. The low-molecular wt polymerase was detected in nuclear extracts and in the soluble fraction. It was resistant to inhibition by N-ethylmaleimide. In all cell types tested, the total DNA polymerase activities were much higher in the cytoplasmic than in the nuclear extracts. Lymphocytes purified from normal peripheral blood had three to four times as much of both polymerase activities per

cell as purified granulocytes. Leukemic myeloblasts had 10-20 times as much cytoplasmic DNA polymerase activity as more mature leukocytes from normal peripheral blood. In general, immature granulopoietic cells contained higher total DNA polymerase activities than more mature granulocytes, the major increases in polymerase activity being in the high- and low-molecular wt cytoplasmic enzymes rather than in the nuclear enzyme.

- 2874 TWO PATTERNS OF NEUTRAL STEROID CONVERSION IN THE FECES OF NORMAL NORTH AMERICANS. (E.) Wilkins, T. D. (Anaerobe Lab., Virginia Polytechnic Inst. State U., Blacksburg) and A. S. Hackman. *Cancer Res* 34(9):2250-2254, 1974.

Neutral steroids extracted from the feces of 31 male and female North Americans on a normal high-meat North American diet were analyzed by gas-liquid chromatography. Sixteen of these subjects were sampled repeatedly over periods of 3-22 months. Among 23 subjects, there was an extensive conversion of cholesterol, sitosterol, and campesterol by the intestinal flora; among the remaining subjects, there was little or no conversion of either cholesterol or the plant steroids by intestinal microorganisms. The conversion patterns were independent of age and sex and were relatively stable over time. The total amounts of both plant and animal steroids excreted by the two groups of subjects were statistically equivalent, and the percentage conversion of cholesterol and sitosterol was essentially equal within each group. The data may point to a more complex relationship between colon cancer risk and fecal steroid conversion than has previously been hypothesized.

- 2875 CONTACT-MEDIATED MYOGENESIS AND INCREASED ACETYLCHOLINESTERASE ACTIVITY IN PRIMARY CULTURES OF MOUSE TERATOCARCINOMA CELLS. (E.) Gearhart, J. D. (Inst. Cancer Res., Fox Chase, Philadelphia, Pa.) and B. Mintz. *Proc Natl Acad Sci USA* 71(5):1734-1738, 1974.

Changes initiated at the cell surface of transplantable mouse teratomas may play some role in promoting early cell differentiation. To establish an *in vitro* system for the experimental investigation of this hypothesis, embryoid body cells were explanted under conditions of cell attachment *versus* suspension and maintained in primary culture. Because cell differentiation in previous reports was relatively limited *in vitro*, the two cellular populations were first compared for genesis of a quantifiable macromolecular phenotype, acetylcholinesterase (AChE) activity, which characterizes several of the cell types most commonly formed at the attached tumors *in vivo*. The attached cells produced markedly increased levels of AChE activity within a few wk, while cells in suspension retained basal levels. AChE was histochemically visualized and was found to occur chiefly in cells undergoing myogenesis, especially during myotube formation. Aberrant muscle fibers formed and became predominant in the cultures. When embryoid bodies were first frac-

tionated by increasing size (which reflects their progressive differentiation), the smallest ones, with relatively more multipotential cells and no apparent muscle cells, also showed increases in AChE in attached cultures. The results are consistent with the view that attachment of the cell surface to a substratum may play a critical role in initiating some cellular developmental commitments, as well as in sustaining the differentiation of cells whose specialization has already been determined. Further experimental modifications of this primary culture system should be useful in analyzing cell-substratum relations and cell-surface changes in early mammalian development.

- 2876 AN ANIMAL MODEL FOR THE STUDY OF SMALL-BOWEL TUMORS. (E.) Coop, K. L. (Coll. Med., U. Iowa, Iowa City), J. G. Sharp, J. W. Osborne and G. R. Zimmerman. *Cancer Res* 34(6):1487-1494, 1974.

An animal model for the study of small-bowel tumors was investigated. Tumors were induced in male Holtzman rats by x-irradiation of only the hypoxic, temporarily exteriorized ileum and jejunum. Following an exposure of 2000 r, 56% of the rats developed adenocarcinoma somewhere in the irradiated segment. Macroscopic metastases were not observed outside the small intestine: however, metastases or direct extensions were observed histologically in the mesentery, pancreas, and abdominal wall. An anemia associated with the intestinal tumors was investigated in detail; the erythrocytes were found to be hypochromic and macrocytic. The anemia appeared to be the result of blood loss from the tumors into the intestinal lumen. Other pathological features associated with these rat intestinal tumors were wt loss, diarrhea, obstruction of the small bowel, and intestinal perforation and hemorrhage. These features are similar to those described in the literature for malignant tumors of the small intestine in humans. This animal model, therefore, would appear to be potentially useful for studies relating to humans with small-bowel tumors.

- 2877 ULTRASTRUCTURAL COMPARISON BETWEEN THE DISTRIBUTION OF CONCAVALIN A AND WHEAT GERM AGGLUTININ CELL SURFACE RECEPTORS OF NORMAL AND TRANSFORMED HAMSTER AND RAT CELL LINES. (E.) Garrido, J. (Inst. Sci. Res. Cancer, Villejuif, France), M.-J. Burglen, D. Samolyk, R. Wicker and W. Bernhard. *Cancer Res* 34(1):230-243, 1974.

A comparative study on the distribution of concanavalin A and wheat germ agglutinin (WGA) receptor sites is presented. Normal hamster cell cultures and an SV40-transformed hamster cell line were used, as were normal rat fibroblasts as well as rat cells transformed by polyoma virus, SV40 virus, and adenovirus 12. The localization of these two lectins on the cell surface is visualized in the electron microscope by means of ultrastructural cytochemistry based on the use of horseradish peroxidase as a marker. The pattern of WGA labeling of normal hamster cells and a cell line transformed by SV40 (Cl₂TSV₅) is

similar to that previously shown for the same material with concanavalin A. Normal hamster cells tend to have a more regular surface reaction, while transformed cells frequently show a discontinuous label. These discontinuities are believed to translate an increased mobility of lectin sites on the plasma membrane. Neither the concanavalin A- nor the wheat germ agglutinin-peroxidase procedure allows one to distinguish normal rat cells from homologous cells transformed by polyoma virus, SV40 virus, or adenovirus 12.

- 2878 CONTROL OF NUCLEAR DIVISION IN NORMAL BUT NOT IN NEOPLASTIC MOUSE CELLS. (E.) O'Neill, F. J. (U. Utah Med. Ctr., Salt Lake City). *Cancer Res* 34(5):1070-1073, 1974.

A control mechanism that limits nuclear division is present in contact-inhibited nontumorigenic mouse BALB/3T3 cells and mouse embryo fibroblasts. In the absence of cytoplasmic division, 3T3 and mouse embryo fibroblast cells may undergo nuclear division once or occasionally twice and then stop. Also, there is no increase in the frequency of premature chromosome condensation. In noncontact-inhibited tumorigenic BALB/3T12 and L-cells, nuclear division occurs repeatedly in the absence of cytoplasmic division and is therefore relatively uncontrolled. The frequency of premature chromosome condensation is markedly increased in 3T12 and L-cells unable to undergo cytoplasmic division. These observations are consistent with the hypothesis that the loss of control of nuclear division in neoplastic cells represents a characteristic defect.

- 2879 DISCONTINUOUS VARIABILITY, IN THE FORM OF A GEOMETRIC PROGRESSION, OF ALBUMIN PRODUCTION IN HEPATOMA AND HYBRID CELLS. (E.) Peterson, J. A. (Lab. Radiobiol., U. California, San Francisco). *Proc Natl Acad Sci USA* 71(5):2062-2066, 1974.

A clonal rat hepatoma cell line (Fu5) produced rat serum albumin at a constant rate over at least 3 months of continuous cultivation. Ten hybrid cell clones derived from the fusion of Fu5 cells with 3T3 mouse fibroblasts and 14 hepatoma subclones of Fu5 cells all produced albumin but at different rates, ranging from 0.09 to 36.7 µg/mg of proteins/72 hr. Despite this variability in albumin production, the distribution of clones was not random but discontinuous, with both the hepatoma and hybrid clones clustering around discrete values which can be fitted into the geometric progression: $a, a(\sqrt{2})^2, a(\sqrt{2})^2, \dots, a(\sqrt{2})^n$ ($a = \text{constant}$). The values of the majority of clones fell into alternate members of this progression, these members differing by a factor of 2. Hepatoma subclones with indistinguishable karyotypes differed in the level of albumin produced by as much as 4-fold. In contrast to the hepatoma clones, albumin production in the hybrid clones decreased with later cell generations. A survey of 28 enzymes in different hepatomas revealed a large variability in enzyme levels which, for most of the enzymes, could be arranged into classes forming a geometric progression. The

apparent widespread nature of this discontinuous phenotypic variability suggests that it may reflect a basic mechanism of control over gene expression in animal cells.

- 2880 GENETIC STUDY OF BREAST CANCER: IDENTIFICATION OF A HIGH RISK GROUP. (E.) Anderson, D. E. (M. D. Anderson Hosp. Tumor Inst., Houston). *Cancer* 34(4):1090-1097, 1974.

Based on a study of 234 breast cancer patients, a group of women was identified whose risk for breast cancer was 47- to 51-fold higher than that of controls. These high-risk women were sisters of patients whose mothers had breast cancer. The disease in these families developed premenopausally, often bilaterally, and was seemingly associated with ovarian function. Since disease susceptibility was transmitted from an affected mother to approximately 30% of her daughters, this early, bilateral form of breast cancer appeared to be strongly heritable. Another, less heritable form was identified in families comprised of at least two affected sisters and unaffected mothers. The risk in these families was 3-fold higher than that of controls, and the disease was primarily postmenopausal, unilateral, and was not strongly associated with ovarian function. No difference was observed in the transmission of breast cancer through paternal and maternal lines of descent.

- 2881 INHIBITION OF CELL PROLIFERATION IN THE LIVERS OF HEPATECTOMIZED RATS BY A RABBIT HEPATIC CHALONE. (E.) Simard, A. (Cancer Inst. Montreal, Canada), L. Corneille, Y. Deschamps, and W. G. Verly. *Proc Natl Acad Sci USA* 71(5):1763-1766, 1974.

A purified chalone isolated from rabbit liver was tested *in vitro* with regenerating rat liver slices incubated with tritiated thymidine to determine more precisely the phase of the normal cell cycle which is blocked by that substance. Biochemical and radioautographic studies showed that the inhibition of ³H-thymidine incorporation during chromosomal DNA replication resulted chiefly from a block in the G₁-S transition in the normal cell cycle. Under these conditions, the chalone had little inhibitory effect on hepatocytes in the S phase of the cycle. The inhibitory effects of the liver chalone appeared to be specific for hepatocytes, and no significant inhibition of cell division was observed when that compound was tested against rat intestinal villi or tongue epithelial cells. When the purified chalone was injected into rats following partial hepatectomy, not only was an inhibition observed during the G₁-S transition, but an increase in the ratio of metaphases to anaphases was found; this suggests that a block also occurs at metaphase as a result of the action of the purified chalone. The injection of a crude supernatant fluid obtained from rabbit liver homogenates into partially hepatectomized rats resulted in a more pronounced block at the G₁-S transition and an inhibition of DNA synthesis during the S phase of the cell cycle. These inhibitory effects were observed in samples of rat intestinal epithelium and tongue epithelial cells as well as hepatocytes.

The rabbit liver supernatant fluid therefore appears to contain one or more nonspecific inhibitors of DNA synthesis in addition to the chalone.

- 2882 GENETICS AND LARGE-BOWEL CANCER. (E.) McKusick, V. A. (Johns Hopkins U. Sch. Med., Baltimore, Md.). *Am J Dig Dis* 19(10):954-958, 1974.

Colon cancer shows a modest familial aggregation which appears to involve a single major genetic factor in at least some families. Inflammatory disease of the bowel, which also displays a modest familial aggregation, predisposes to malignancy. Although the familial aggregation displayed by colon cancer is apparently independent of hereditary polyposis, the best established genetic factors in large-bowel cancer are those responsible for hereditary polyposis. Among the various types of polyps, the main malignant potential resides with adenomatous polyps, the hereditary form of which is divided into two main disorders: familial polyposis coli, and the Gardner syndrome. The relationship between genetics and cancer of the colon may be clarified by information regarding the relative frequencies of these disorders, the number and distribution of polyps in the two conditions, and whether or not there are subcategories within these two major recognizable disorders. Information is also needed regarding the possibility of other hereditary polyposis states, the relation between age and the number of polyps (does it vary from family to family?), the behavior of familial polyposis in relation to the polyps and to the development of cancer in low-bowel-cancer areas of the world, the percentage of all bowel cancer accounted for by these defined hereditary disorders, and the connection between gene and phenotype in the various forms of hereditary polyposis.

- 2883 BIOCHEMICAL CHARACTERIZATION OF CANCER CELLS *IN VITRO* PART II. SOME ENZYME LEVELS OF THE GLYCOLYTIC AND HEXOSEMONOPHOSPHATE PATHWAYS IN NORMAL AND MALIGNANT HUMAN CELLS *IN VITRO*. (E.) Talageri, V. R. (Biol. Div., Cancer Res. Inst., Tata Mem. Ctr., Bombay, India), A. G. Ravishankar and K. J. Ranadive. *Indian J Cancer* 10(4):428-435, 1973.

The levels of aldolase, lactic dehydrogenase, hexokinase, glucose-6-phosphate dehydrogenase, and 6-phosphogluconate dehydrogenase activity in normal human embryonic skeletal muscle strains were compared with those in similar cell strains in which malignant transformation was induced by single exposure to urethan (10 or 5 mg/ml) or 3:4 benzopyrene (BP, 10 µg/ml). None of the untreated human fibroblasts was tumorigenic when injected into the cheek pouches of hamsters, while all of the treated cells produced tumors within 4-16 days. Compared with the untreated cells, aldolase activity was increased 3.5-4.0 and 2.5-3.0 times in the urethan and BP treated cells, resp. Lactic dehydrogenase activity was increased 2-5.4 times in the transformed group and the 6-phosphogluconic dehydrogenase activity was significantly lower in the transformed cells. The activities of hexokinase and glucose 6-phosphate dehydrogenase were unchanged in the transformed cells.

- 2884 ULTRASTRUCTURAL AND BIOCHEMICAL STUDIES OF THE ISOLATED FIBRILLAR COMPONENT OF NUCLEOLI FROM NOVIKOFF HEPATOMA ASCITES CELLS. (E.) Daskal, Y. (Baylor Coll. Med., Houston, Tex.), A. W. Prestayko and H. Busch. *Exp Cell Res* 88(1):1-14, 1974.

Nucleoli of Novikoff hepatoma ascites cells were fractionated into granular and fibrillar components with solutions containing polyvinylsulfate and Mg^{2+} (PVS/ Mg^{2+}) or solutions containing EDTA. After treatment with the PVS/ Mg^{2+} solutions, the morphology of the fibrillar component was similar to that *in situ* inasmuch as they contain fibrillar clusters as well as other fibrillar elements ranging in diameter from 150-700 Å. The nucleotide composition of the RNA of the fibrillar and granular fractions was similar to that of ribosomal RNA. In agreement with earlier autoradiographic studies, the kinetics of incorporation of ^{32}P -orthophosphate into the RNA in both fractions showed that the specific activity of the RNA of the fibrillar fraction was 4-fold greater than that of RNA in the granular region at 15 min. After 2 hr the specific activity of the RNA in the granular region was 1.5 times greater than that in the fibrillar region. Two-dimensional polyacrylamide gel electrophoresis showed that the fibrillar fraction contained fewer proteins than the granular fraction. Some of the proteins were common to both the nucleolar granular particles and cytoplasmic ribosomes while others appeared to be unique to this fraction.

- 2885 REGULATION OF MELANOCYTE STIMULATING HORMONE ACTION AT THE RECEPTOR LEVEL: DISCONTINUOUS BINDING OF HORMONE TO SYNCHRONIZED MOUSE MELANOMA CELLS DURING THE CELL CYCLE. (E.) Varga, J. M. (Yale U. Sch. Med., New Haven, Conn.), A. Dipasquale, J. Pawelek, J. S. McGuire and A. B. Lerner. *Proc Natl Acad Sci USA* 71(5):1590-1593, 1974.

Melanocytes of the Coudman mouse melanoma line (NCTC 3960, CC1 53) were grown in culture; the cells were arrested in mitosis with colchicine. At various times after their release from colchicine, the cells were incubated with ^{125}I -labeled melanocyte stimulating hormone (MSH). MSH coupled with Sepharose effected an increase in the tyrosinase activity of the cultivated melanoma cells. Synchronized cells responded to the MSH only in the G2 phase of the cell cycle, although their response to cyclic AMP was independent of their position in the cell cycle. The binding of ^{125}I -labeled MSH occurred predominantly in the G2 phase. The MSH acted at the cell membrane. These observations are explained by a model in which the hormone can activate adenylate cyclase by binding to a MSH receptor only in G2; the events distal to cyclic AMP production can occur throughout the cell cycle.

- 2886 ENZYME ACTIVITY IN INVASIVE TUMORS OF HUMAN BREAST AND COLON. (E.) Bosmann, H. B. (U. Rochester Sch. Med. Dent., N.Y.) and T. C. Hall. *Proc Natl Acad Sci USA* 71(5):1833-1837, 1974.

The levels of glycoprotein:glycosyl transferases, glycosidases, and proteases were assayed in human

malignant neoplastic tissues (15 invasive mammary carcinomas, 3 noninvasive mammary carcinomas, and 7 infiltrative colon carcinomas), human benign tumor tissues, and normal tissues from tumor patients. In each case, sialyltransferase levels in the malignant tissues were greatly elevated compared with those in the normal tissues; this was particularly true of the breast tumor tissues. This increase was not due to the cell density of the tissue. The levels of β -galactosidase, α -mannosidase, and protease (pH 3.4) were significantly elevated in both the breast and colon carcinoma tissues, while the levels of acid phosphatase and β -N-acetylgalactosaminidase were significantly elevated in the breast carcinoma tissues and the levels of neuraminidase were significantly elevated in the colon carcinoma tissues. In five patients with fibrocystic disease, the levels of β -N-acetylgalactosaminidase, β -N-acetylglucosaminidase, and protease (pH 3.4) were elevated. The increase in transferase activity may be associated with altered membrane synthesis in the neoplastic state; changes in the activity of degradative enzymes may be associated with tumor invasiveness and maintenance of the neoplastic state. Measurements on human tumors are possibly more directly relevant to human carcinogenesis than those described from transformed fibroblastic cells *in vitro*.

- 2888 A COMPARISON OF PHENYLALANYL-tRNA SYNTHETASE FROM RAT LIVER AND MINIMAL DEVIATION HEPATOMA. (E.) Ouellette, A. J. (Harvard Med. Sch., Boston, Mass.) and M. W. Taylor. *Cancer Res* 34(7):1636-1642, 1974.

Phenylalanyl-transfer RNA synthetase was purified from rat liver and Morris hepatoma 5123D, and the properties of the enzymes compared. Using ammonium sulfate fractionation, and chromatography on DEAE-cellulose and brushite, the liver and hepatoma enzymes were purified 240- and 275-fold, resp. The two enzymes were chromatographically indistinguishable, and only one peak of enzyme activity was evident in either tissue. The liver and hepatoma enzymes exhibited similar heat-inactivation kinetics at 50 C, and the apparent Michaelis constants for the substrates of the enzymes were identical. All parameters measured in comparing the enzymes failed to reveal functional differences. The inference drawn is that the liver enzyme has been conserved during the neoplastic transformation to the hepatoma. This study represents the first direct comparison of aminoacyl-transfer RNA synthetases from a minimal deviation hepatoma and liver.

- 2887 DIFFERENCES IN MEMBRANE FLUIDITY AND STRUCTURE IN CONTACT-INHIBITED AND TRANSFORMED CELLS. (E.) Barnett, R. E. (Dept. Chem., U. Minnesota, Minneapolis), L. T. Furcht and R. E. Scott. *Proc Natl Acad Sci USA* 71(5):1992-1994, 1974.

Contact-inhibited Balb/c and Swiss 3T3 mouse fibroblasts and simian virus 40 (SV), polyoma virus (PY), murine sarcoma virus (MSV), and methylcholanthrene (MC)-transformed Balb/c 3T3 fibroblasts were freeze-fractured by glycerination. The organization of the

plasma membrane lipids in the contact-inhibited and transformed 3T3 fibroblasts was probed with the spin label sodium 6-(4',4'-dimethyloxazolidinyl-*N*-oxyl)-heptadecanoate (I). Ultrastructural studies showed that the contact-inhibited cells had ordered membrane lipids and aggregated intramembranous particles, whereas the transformed cells had fluid membrane lipids and randomly distributed intramembranous particles. These data suggest a model for the regulation of certain cell membrane activities. According to the model, agents which change the fraction of the membrane lipids in the fluid state will of necessity change the distribution of the membrane proteins between the liquid and ordered region of the membrane lipids. Based on this model, the control of cell growth in general may be dependent on modulation in the organization of the cell membrane. In particular, differences in the growth characteristics of normal and transformed cells may be due to primary changes in membrane fluidity and structure which modulate the activity of membrane enzymes, which, in turn, are critical to the regulation of cellular proliferation.

2889 ENDOCRINE DISORDERS AS A CONTRIBUTORY FACTOR TO NEOPLASIA IN SJL/J MICE. (E.)

Pierpaoli, W. (Swiss Res. Inst., Med. Dept., Davos-Platz), N. Haran-Ghera, E. Bianchi, J. Muller, A. Meshorer and M. Bree. *J Natl Cancer Inst* 53(3): 731-744, 1974.

The endocrine status of SJL/J mice, which develop a high incidence of spontaneous reticulum cell sarcomas or neoplasms at an early age, was studied. Light and electron microscopy revealed that the adeno-hypophyses of both sexes became progressively infiltrated (with increasing age) with an abnormal number of gonadotropin-producing cells which probably secreted large amounts of luteotropic hormone. The ovaries had numerous large corpora lutea even in animals over 1 yr of age with reticulum cell neoplasms. The adrenal cortexes of the female mice showed no regression of the reticular zone. In accordance with the anomalous condition of the adeno-hypophysis and ovaries, the females had abnormal estrous cycles, with prolonged diestrus and consequent reductions in fertility. In 6-month-old male SJL/J mice, the level of testosterone in the serum was far higher than in C57BL/6 males of the same age. This supports the concept of a pathologic and progressively increasing high input of gonadotropins in SJL/J mice. The role of hormones in the development of systemic neoplasms and in leukemic virus expression is discussed.

2890 PREGNANCY DEPENDENCE OF MAMMARY TUMORS IN STRAIN DDD MICE. (E.) Matsuzawa, A.,

(Inst. Med. Sci., U. Tokyo, Japan), T. Yamamoto and K. Suzuki. *J Natl Cancer Inst* 52(3):449-456, 1974.

Mammary tumors, which developed in 22 of 2411 strain DDD retired breeder mice under 12 months of age, were transplanted into virgins. Half the recipients

were bred so that the tumors could be examined for pregnancy dependence: four were classified as completely pregnancy-dependent (CPD), two as moderately pregnancy-dependent (MPD), three as slightly pregnancy-dependent (SPD), and 13 as pregnancy-independent (PID). The CPD tumors did not grow in virgins but grew rapidly in pregnant breeders and regressed after parturition, reaching ascending peaks in successive pregnancies. Morphologically, all CPD tumors were classified as type A. One MPD tumor was type A and the other, a pale-cell carcinoma. Two type A + B and 1 type P were SPD. PID tumors consisted of three type A + B, five type P, three pale-cell carcinomas, and two mixed tumors. These findings suggest that the mammary tumor virus (MTV) of strain DDD may belong to plaque-forming mammary tumor virus.

2892 CYTOGENETIC STUDIES IN MULTIPLE MYELOMA.

(E.) Anday, G. J. (VA Wadsworth Hosp. Ctr., Los Angeles, Calif.), B. Fishkin and E. P. Gabor. *J Natl Cancer Inst* 52(4):1069-1079, 1974.

The chromosomes in bone marrow specimens from multiple myeloma (MM) patients were studied to determine the frequency and diversity of chromosomal abnormalities and to correlate them with serum and/or urine paraproteins, clinical course of the disease, and the effect of therapy. Chromosome abnormalities were found in 70 specimens of 38 MM patients. Structural abnormalities were insignificant except for marker chromosomes in 11 patients. Numerical abnormalities ranged from hypodiploidy to hyperdiploidy and clones were recognized in seven patients. The diversity of cytogenetic findings without any specificity for MM or its differing product places this hematologic neoplasm into the group of solid malignant tumors without specific chromosome changes. The chromosome changes varied during treatment. Remission was associated with increased diploidy and hypodiploidy and relapse with decreased diploidy and increased hyperdiploidy. Comparison of initial studies with subsequent chromosome studies was valuable in the assessment of the patients' condition.

2891 ELEVATED CYCLIC AMP LEVELS IN HUMAN BREAST-CANCER TISSUE. (E.) Minton, J. P. (Dept.

Surg., U. Hosp., Ohio St. U., Columbus), T. Wisenbaugh and R. H. Matthews. *J Natl Cancer Inst* 53(1):283-284, 1974.

Tracer amounts of ³H-cyclic AMP were added to extracts from malignant and benign human breast tumors and normal breast tissue. The samples were subsequently tested for cyclic AMP by radioimmunoassay. The cyclic AMP levels were 15 times higher in the cancer tissues than in the normal breast tissues and 10 times higher than in the benign fibrocystic breast samples; these differences were statistically significant at the 0.01 level. The high levels of cyclic AMP may represent a situation analogous to that in which a deficiency in cyclic AMP binding protein and in cyclic AMP-dependent protein kinase activity makes a population of lymphoma cells resistant to the cytolytic effects of dibutyryl cyclic AMP. In any event, the results

obtained should not be interpreted as a negation of the concept that cyclic AMP represses growth and promotes the differentiation of normal tissue.

- 2893 NEOPLASMS, DIFFERENTIATIONS AND MUTATIONS. (E.) Pierce, G. B. (Dept. Pathol., U. Colorado Med. Ctr., Denver). *Am J Pathol* 77(1):103-118, 1974.

Evidence is presented to support the concept that malignant tumors are postembryonic differentiations superimposed on the process of tissue maintenance and renewal. Malignant stem cells are derived from normal stem cells. They have a capacity for proliferation and differentiation that operates at a different level of control than the normal. Even so, malignant stem cells are responsive to environmental control, suggesting that it may be possible to direct their differentiation or at least to control their ability to replicate. A tumor is a caricature of normal tissue and appears undifferentiated because of the preponderance of undifferentiated proliferating stem cells in relationship to the number of cells that have differentiated and become benign.

- 2894 CONCERNING A FAMILIAL ASSOCIATION BETWEEN BREAST CANCER AND BOTH PROSTATIC AND UTERINE MALIGNANCIES. (E.) Thiessen, E. U. (Prev. Med. Inst.-Strang Clin., New York, N.Y.). *Cancer* 34(4):1102-1107, 1974.

The familial incidence and distribution of all malignancies were determined for a group of 145 female breast cancer patients and 139 randomized control patients. The cancer patients and controls did not differ significantly in terms of age, socioeconomic status, or education. In general, both family size and amount of family medical history available were comparable between the two groups. The incidences of breast cancer, uterine cancer, and prostatic cancer were significantly higher among the families of the breast cancer patients than among the control families. Although ovarian and cervical cancers were 3-fold more common among family members of cancer patients relative to control patients, the numbers were too small to determine statistical significance. The data suggest the influence of some type of genetic factor or combination of genetic and nongenetic factors. The expression of this factor could lie in some variance in the hormone(s) produced and/or a common abnormality in the target organ receptor site.

- 2895 GROWTH CONTROL IN CULTURED MOUSE FIBROBLASTS: INDUCTION OF THE PLEIOTYPIC AND MITOGENIC RESPONSES BY A PURIFIED GROWTH FACTOR. (E.) Rudland, P. S. (Salk Inst. Biol. Sci., San Diego, Calif.), W. Seifert and D. Gospodarowicz. *Proc Natl Acad Sci USA* 71(7):2600-2604, 1974.

Addition of serum to quiescent mouse fibroblasts induced a series of macromolecular changes (a pleiotypic response) followed by DNA synthesis and cell division. A new pituitary hormone, fibroblast growth

factor, and hydrocortisone acting at physiological concentrations could completely replace exogenously added serum for the induction of these events in lines of BALB/c 3T3 cells. The induction of cell growth was specific for cultured fibroblasts; no stimulation was observed for mouse epithelial cells or virally transformed fibroblasts.

- 2896 SPECIFIC BINDING OF NERVE GROWTH FACTOR (NGF) BY MURINE C 1300 NEUROBLASTOMA CELLS. (E.) Revoltella, R. (Lab. Cell Biol., Natl. Res. Council, Rome, Italy), L. Bertolini, M. Pediconi and E. Vignetti. *J Exp Med* 140(2):437-451, 1974.

The nerve growth factor (NGF), a protein capable of inducing differentiation of sympathetic nerve cells, binds readily with the membrane surface of murine C 1300 neuroblastoma cells. The total binding capacity of NGF by the cells was quantitatively measured by a radioimmunoassay technique. An average number of 10^6 molecules of NGF could be bound, at saturation, by each cell with an average relative association constant of about 10^7 liters/mol. Experiments with synchronized cells, showed that either the number of molecules of bound ligand or the avidity of the binding interaction between NGF and cells varied depending on their growth cycle, the maximal binding occurring during the G₁ and early S phase. Binding of 125 I-NGF was suppressed by trypsin treatment of the cells; new receptor sites, however, were rapidly replaced onto the membrane surface within 1-2 hr. Cells exposed to 3 M KCl released into the supernatant a protein product exhibiting similar high avidity for NGF. Antibodies made specific to this protein were capable, in the absence of complement, of inhibiting the binding of 125 I-NGF by the cells and in the presence of complement they killed them.

- 2897 CHROMOSOMES AND CAUSATION OF HUMAN CANCER AND LEUKEMIA. IX. PROGNOSTIC AND THERAPEUTIC VALUE OF CHROMOSOMAL FINDINGS IN ACUTE MYELOBLASTIC LEUKEMIA. (E.) Sakurai, M. (Roswell Park Memorial Inst., Buffalo, N.Y.) and A. A. Sandberg. *Cancer* 33(6):1548-1557, 1974.

The median survival after initiation of antileukemic therapy of 88 patients with acute myeloblastic leukemia (AML) was surprisingly short for 15 patients who never had normal metaphases in their bone marrow during the course of the disease (AA patients, 1.2 months), particularly when compared to the survival of 26 patients with both abnormal and normal metaphases (AN patients, 7.2 months) or 47 with only normal metaphases (N patients, 9.1 months). Among the latter two groups, the majority of patients over 70 yr of age had a very poor survival after therapy (0.7 months). The remarkable shortness of the life span of these patients after therapy, as compared to that from the onset of symptoms, indicates that current therapy is of little help to AA patients and most of the patients over 70. Some of the AA patients and a few of the AN patients constitute a unique group of AML patients in whom the erythroid and myeloid series are involved by the leukemic process and who are thus actually affected by erythroleukemia.

Their survival, however, seems to depend on whether or not they have any normal metaphases in their bone marrow, eligible to repopulate the marrow with normal cells when the leukemic ones have responded to therapy.

2898 EXPRESSION OF NEURONAL PHENOTYPES IN NEURO-BLASTOMA CELL HYBRIDS. (E.) McMorris, F.

A. (Wistar Inst., Phila., Pa.) and F. H. Ruddle. *Dev Biol* 39(2):226-246, 1974.

Four series of neuroblastoma cell hybrids were isolated, using as parental cells a human and a mouse neuroblastoma, a human fibroblast, and a mouse L cell line. Hybrid clones were analyzed for karyotype, morphology, acetylcholinesterase, and choline acetyltransferase. Acetylcholinesterase activity, which was present in the neuroblastoma parents but absent in the fibroblasts, showed continued expression in all series of hybrids, and neuronal morphology was expressed in three of the four hybrid series. Choline acetyltransferase, which mediates acetylcholine synthesis in cholinergic neurons, was absent from all parents and hybrids except for one hybrid clone, in which expression of the enzyme was activated. These results are compared with previously published data on assays of the same hybrids for additional neuronal phenotypes. These phenotypes are electrical excitability and acetylcholine sensitivity, presence of the neuron-specific 14-3-2 protein and steroid sulfatase, and glycosphingolipid composition. Among those phenotypes which continue to be expressed, the level of expression is closely correlated with acetylcholinesterase specific activity and with chromosome number.

2899 ROLE OF DNA-DEPENDENT RNA POLYMERASE III IN THE TRANSCRIPTION OF THE tRNA AND 5S

RNA GENES. (E.) Weinmann, R. (Div. Biol. Biomed. Sci., Washington U., St. Louis, Mo.) and R. G. Roeder. *Proc Natl Acad Sci USA* 71(5):1790-1794, 1974.

Mouse myeloma cells contain two chromatographically distinct forms of RNA polymerase III (designated III_A and III_B). The enzymes are unaffected by low α -amanitin concentrations which completely inhibit RNA polymerase II, but they exhibit characteristic inhibition curves at higher toxin concentrations. RNA polymerase I is unaffected by any concentration of α -amanitin. Myeloma RNA polymerases II, III_A, and III_B appear to be inhibited by the same mechanism, since the toxin rapidly blocks chain elongation by each enzyme. Isolated myeloma nuclei and nucleoli continue to synthesize RNA *via* the endogenous RNA polymerases when incubated *in vitro*. With nuclei, newly synthesized 4S precursor (pre-4S) and 5S RNA species were detected by electrophoretic analysis of the total nuclear RNA or the RNA released into the supernatant during incubation. The synthesis of both pre-4S and 5S RNA species was inhibited by α -amanitin, but only at high concentrations; the α -amanitin inhibition curves for these RNAs were identical to those obtained for solubilized RNA polymerases III_A and III_B. The endogenous RNA polymerase II activity of the isolated nuclei was inhibited by α -amanitin in concentrations required to inhibit purified enzyme II. However, 40-50% of the endogenous activity of the nuclei and 100% of

the endogenous activity of the purified nucleoli were completely resistant to the high α -amanitin concentrations needed to inhibit the RNA polymerase III activities. These data rule out nonspecific inhibitory effects in the endogenous systems, and unequivocally demonstrate the role of RNA polymerase III_A and/or III_B in the synthesis of (pre) 4S RNAs and a 5S RNA species.

2900 THE FINE STRUCTURE OF THE NUCLEOLUS DURING INTERPHASE AND MITOSIS IN EHRlich TUMOUR CELLS CULTIVATED *IN VITRO*. (E.) Goessens, G. (Inst. Histologie, U. Liege, Belgium) and A. Lepoint. *Exp Cell Res* 87(1):63-72, 1974.

The nucleoli of hypertetraploid Ehrlich ascites tumor cells grown *in vitro* were examined by electron microscopy. During the interphase, the nucleoli contain fibrils (pars fibrosa), granules (pars granulosa), and areas of low electron density (fibrillar centers). The pars fibrosa and pars granulosa disappear during prophase, but the fibrillar centers remain visible. The latter, associated with the chromosomes, persist throughout the entire mitosis. In late telophase, these nucleolar bodies are situated inside the daughter nuclei, and progressively become surrounded by the pars fibrosa and pars granulosa. These observations suggest that some nucleolar material is transmitted from one cell generation to the next. This material could not be related to the nucleolar organizers.

2901 TUMOR ANGIOGENESIS FACTOR. (E.) Folkman, J. (Children's Hosp. Med. Ctr., Boston, Mass.). *Cancer Res* 34(8):2109-2113, 1974.

Evidence from recent studies indicates that solid tumor growth is not continuous but that it can be separated into two stages, avascular and vascular. In the avascular stage, tumors remain dormant at diameters of 1 to 2 mm. Further growth is possible only after new capillaries have been elicited from the host and have penetrated the tumor. This capillary proliferation is stimulated by a diffusible factor, tumor angiogenesis factor, released by solid tumors, and by neoplastic cells in culture. The biology and isolation of tumor angiogenesis factor are reviewed. Evidence for the mechanism of tumor dormancy in the absence of angiogenesis is presented and therapeutic implications of the inhibition of tumor angiogenesis are mentioned briefly.

2902 PITUITARY PROLACTIN LEVELS IN CANINE MAMMARY CANCER. (E.) Saluja, P. G. (Dept. Exp. Pathol. Cancer Res., U. Leeds, England), J. M. Hamilton, M. Gronow and W. Misdorp. *Eur J Cancer* 10(2):63-66, 1974.

The prolactin content of the adenohypophysis of 19 bitches (mean age 11.8 yr) with spontaneous mammary tumors was estimated densitometrically after isoelectric focusing in polyacrylamide gel columns and staining with Coomassie brilliant blue. As a group, the bitches with mammary tumors had significantly

higher pituitary prolactin concentrations than normal bitches of comparable endocrine state. This difference was somewhat more significant among diestrous bitches than among estrous-leuteal-spayed animals. The elevated prolactin levels were confined to those animals with carcinomas. It is unlikely that age influenced the pituitary prolactin concentrations in this study. The data indicate that prolactin may be of importance in mammary neoplasia in the dog.

- 2903 INFLUENCE OF NURSING ON THE RELEASE OF PROLACTIN AND GH IN MICE WITH HIGH AND LOW INCIDENCE OF MAMMARY TUMORS. (E.) Sinha, Y. N. (Scripps Clin. Res. Fdn., La Jolla, Calif.), C. B. Salocks, U. J. Lewis and W. P. Vanderlaan. *Endocrinology* 95(4):947-954, 1974.

Experiments designed to compare the release of prolactin (PRL) and growth hormone (GH) in response to nursing in a mammary tumor-susceptible (C3H/St) and a tumor-resistant strain (C57BL/St) of mice using radioimmunoassay techniques are reported. The influence of nursing on GH release in the Sprague-Dawley rat was also investigated. Prolactin was released in great quantities in mice of both strains. Serum PRL concentrations after nursing were generally lower in C3H/St mice than in C57BL/St mice. The data suggest greater PRL metabolism by C3H/St mice than by C57BL/St mice. The concentration of GH in serum usually decreased or remained unchanged after nursing in mice of both strains and in rats. Changes in GH concentration of the pituitary seemed dependent upon the method of extraction but no significant differences in GH concentration were detected between nursing and non-nursing mice or rats by radioimmunoassay, bioassay, or disc electrophoresis. The results demonstrate that nursing does not induce release of radioimmunoassayable GH in mice or rats despite concurrent release of PRL.

- 2904 DIETARY FIBER AND DISEASE. (E.) Burkitt, D. P. (Med. Res. Council External Sci. Staff, London, England), A. R. P. Walker and N. S. Painter. *JAMA* 229(8):1068-1074, 1974.

Many diseases common in and characteristic of modern western civilization have been shown to be related to the amount of time necessary for the passage of intestinal content through the alimentary tract, and to the bulk and consistency of stools. These factors have in turn been shown to be greatly influenced by the fiber content of the diet and by the amount of cereal fiber in particular. Mechanisms are postulated whereby these changes in gastrointestinal behavior could in part explain the occurrence of such common disorders as ischemic heart disease, appendicitis, diverticular disease, gallbladder disease, varicose veins, deep vein thrombosis, hiatal hernia, and tumors of the large bowel. Intestinal transit time, intracolonic pressure level, number and type of fecal bacteria, serum cholesterol level, and changes in bile salt metabolism are all related to the amount of dietary fiber consumed. The fecal arrest and small stool mass associated with a low-

fiber diet may influence development of malignant and benign small-bowel tumors by facilitating bacterial degradation of bile salts.

- 2905 ELEVATED LEVELS OF ENDOMETRIAL LACTATE DEHYDROGENASE IN HYPERPLASIA AND CARCINOMA OF HUMAN ENDOMETRIUM. (E.) Fottrell, P. F. (Dept. Biochem., U. Coll., Galway, Ireland), C. M. Spellman and E. M. O'Dwyer. *Cancer Res* 34(5):979-980, 1974.

Endometrial biopsies were taken from 43 patients aged 18-40 yr who were under investigation for menstrual abnormalities. Of these patients, 34 had hyperplastic nonsecretory endometrium and 9 had cystic hyperplasia of endometrium. Total lactate dehydrogenase (LDH) levels were greatly increased in all cases of hyperplastic endometrium when compared with normal values. The levels were even higher in three cases of endometrial carcinoma. The percentage of LDH-M subunits in the hyperplastic endometrium cases was 5-6 times higher than normal. High concentrations of LDH-M subunits were also seen in the endometrial carcinoma cases. The data suggest a biochemical relationship between hyperplasia and carcinoma of the endometrium.

- 2906 MICROWAVE CHARACTERISTICS OF HUMAN TUMOR CELLS. (E.) Stamm, M. E. (U. California Sch. Med., Los Angeles), W. D. Winters, D. L. Morton and S. L. Warren. *Oncology* 29(4):294-301, 1974.

Microwave energy transmitted between 76 and 86 GHz was used to identify differences between human tumor cells and normal cells grown in tissue cultures. Unique differential transmission spectra were demonstrated when various types of cultured malignant cells were compared with their autologous counterparts. Tumor samples of the same histologic type, although from different patients, had the same differential transmission spectra in the region of 76-86 GHz. Differences between the microwave spectra of normal cells of the same histologic type were observed in samples from different patients. The differences in heights of the peaks along the spectrum appeared to give an indication of the amount of tumor cells *versus* normal cells in the tumor sample.

- 2907 BIOCHEMICAL DIFFERENTIATION OF A MURINE NEUROBLASTOMA *IN VITRO* AND *IN VIVO*. (E.) Ruffner, B. W., Jr. (U. Virginia Sch. Med., Charlottesville) and D. M. Grieshaber. *Cancer Res* 34(3):551-558, 1974.

Two cell lines were cloned from murine neuroblastoma C-1300, and their behavior was compared in tissue culture and *in vivo*. The lines were easily distinguished *in vitro* by differences in morphological behavior and biochemical changes during growth. One line, designated N-18, stopped growing with fewer cells/plate and developed more axon-like processes than the other line, N-103. N-18 contained more acetylcholinesterase (AcChE) than N-103, and the specific activity of AcChE increased greatly during

the stationary phase of growth. The two cell lines injected into syngeneic A/Jax mice grew at the same rate and killed the hosts in approximately the same time. The morphological differences were not present, but the specific activity of AcChE remained higher in N-18 and increased as the tumor grew. The findings were not altered after correction was made for tumor necrosis by comparing AcChE levels with levels of lactic dehydrogenase in the same homogenates. Inhibition curves showed that the enzyme studied is "true" AcChE (EC 3.1.1.7) rather than nonspecific cholinesterase (EC 3.1.1.8). The biochemical characteristics seen *in vitro* are retained when the tumors are grown in animals, but the behavior in tissue culture cannot be related directly to the differences in malignancy *in vivo*.

2908 DIURNAL DISTRIBUTION OF MOTOR ACTIVITY AND FEEDING DURING GROWTH OF TUMORS. (E.)

Morrison, S. D. (Nat'l. Cancer Inst., Bethesda, Md.). *Cancer Res* 34(7):1632-1635, 1974.

The diurnal distributions of motor activity and feeding were examined as indicators of hypothalamic function in three host-tumor organisms: (a) Sprague-Dawley-Walker 256 carcinosarcoma, (b) Sprague-Dawley-4M carcinoma, and (c) Buffalo-5123 hepatoma. The normal, high night/day activity ratio was depressed with growth of tumor in b, but there was no significant change in a and c. The normal, high night to day feeding ratio was depressed with growth of tumor in a, reduced to one in b, and slightly enhanced in c. Changes in diurnal ratios preceded decline in total daily food intake and motor activity. Magnitudes of diurnal ratios of activity and feeding were unrelated in nontumor-bearing animals. Immediately upon initiation of growth of all tumors, the two ratios became significantly correlated, even when there was no significant change in average magnitude. Hypothalamic dysfunction may be slightly but variably involved in cachectic hypophagia.

2909 IMBALANCE IN ORNITHINE METABOLISM IN HEPATOMAS OF DIFFERENT GROWTH RATES AS EXPRESSED IN BEHAVIOR OF L-ORNITHINE:2-OXOACID AMINOTRANSFERASE (ORNITHINE TRANSAMINASE, EC 2.6.1.13). (E.) Tomino, I. (Indiana U. Sch. Med., Indianapolis), N. Katunuma, H. P. Morris and G. Weber. *Cancer Res* 34(3):627-636, 1974.

The ornithine transaminase (EC 2.6.1.13) concentration in normal ACI/N and Buffalo rat liver and in s.c. transplanted rat hepatomas of different growth rates was determined by two independent methods, enzymatic assay of activity and immunotitration of enzyme amount. Kinetic studies showed that the enzyme preparations from normal liver and hepatoma were indistinguishable on the basis of their pH optima, kinetic properties for substrates, and intracellular distribution. Electrophoretic studies, using the acrylamide gel disc method, indicated that the purified ornithine transaminase from liver, from slowly growing hepatoma 44, and from rapidly growing hepatoma 7777 had the same mobility. Immunotitration showed that the en-

zymes in liver and hepatomas were immunologically identical. The concentration of ornithine transaminase in the rapidly growing hepatomas was markedly decreased, indicating a decline in the potential of such neoplasms to channel ornithine into the synthesis of glutamic γ -semialdehyde and L-glutamate. In the regenerating liver at 24 hr after partial hepatectomy, the enzyme activity was in the same range as that of the sham-operated controls. Since the regenerating liver proliferates at a rate comparable to that of the rapidly growing hepatomas, the markedly decreased activity observed in such tumors appeared to be specific to neoplastic cell growth.

2910 ANALYSIS OF Q-BANDING PATTERNS IN HUMAN CELL LINES. (E.) Lin, C. C. (Med. Fac., U. Calgary, Alberta, Canada) and S. Goldstein. *J Nat'l Cancer Inst* 53(2):298-304, 1974.

Chromosome analysis by Q-banding was done on three human cell lines, HeLa, KB, and Hep-2. Excess chromosome material and several marker chromosomes were found in cells from these three lines. Certain chromosomes were frequently present in triplicate or quadruplicate, which suggested that these chromosomes bore certain gene(s) controlling cell growth *in vitro* and that increased gene dosage created a selective growth advantage. The many identifiable chromosome variations in these cells suggested their use for somatic cell hybridization studies aimed at mapping human genes on regions within specific chromosomes. However, the observations that three markers appeared identical in the three cell lines, the nonrandom representation of certain chromosomes, and the presence in all lines of the glucose-6-phosphate dehydrogenase A electrophoretic variant and the normal phosphoglucomutase type 1 pattern substantiate the idea that these cell lines were derived as contaminants from HeLa cells.

2911 SEVERAL CHANGES ASSOCIATED WITH THE ACQUISITION OF A SINGLE CHROMOSOME IN RAT GLIAL TUMOR CELLS. (E.) Roscoe, J. P. (Middlesex Hosp. Med. Sch., London, England) and B. E. Gibbs. *J Nat'l Cancer Inst* 53(2):581-583, 1974.

Two subcultures of a cell line derived from a rat glial tumor diverged in their properties when grown in medium containing different concentrations of fetal calf serum. Changes were noted in their morphology, response to treatment with dibutyryl cyclic adenosine monophosphate, and plating efficiency in soft agar. One subculture had a less "transformed" phenotype than the other. This culture also underwent a change in karyotype; it no longer had the diploid number of 42 chromosomes but a modal number of 43 chromosomes. Both subcultures were tumorigenic and gave histologically identical tumors with a similar latent period. A tumor derived from the less transformed culture had a modal chromosome number of 42. Thus, possibly transformed properties in both cultures were expressed only by cells with a 42-chromosome karyotype. Reversal of the initial change in serum concentration had no further effect, the subcultures remaining true to their parental type.

2912 HETEROTRANSPLANTATION MODEL OF HUMAN MALIGNANT MELANOMA. (E.) Mukheyi, B. (New Engl. Med. Ctr. Hosp., Boston, Mass.), A. Flowers, L. Nathanson and D. A. Clark. *Cancer Res* 34(1):43-46, 1974.

A heterotransplantation model of human melanoma has been established in immunosuppressed Wistar-Furth rats. Heterotransplantation was accomplished by s.c. inoculation of live cultured human melanoma cells in Wistar-Furth neonates immunosuppressed with antithymocyte serum. Two different tumor cell lines (BeRo and HaLe) have been transplanted, and the BeRo line has been maintained through serial transplantation for up to 12 generations. The transplanted BeRo tumor line produced pigment, and both lines exhibited an aneuploid karyotype with the banding characteristics of human chromosomes. Multiple pulmonary metastases have been noted in one animal bearing a s.c. (BeRo) tumor transplant. Membrane immunofluorescence studies with autologous and allogeneic human sera revealed discrete sites of cross-reacting antigen(s) on cell membrane of the melanoma cells both prior to and after heterotransplantation. Appreciable augmentation in the antigenicity of cell membrane characterized by an increased number of sites of immune complexes or by a complete ring of fluorescence was observed with the animal-passaged cells as opposed to fewer sites of immune complexes on the cultured cells. Sera from several tumor-bearing rats also revealed circulating antibody directed against antigen(s) on transplanted melanoma cells, and often demonstrated cross-reaction with cells derived from several other melanoma cell lines.

2913 HUMAN CHROMOSOME 21 DOSAGE: EFFECT ON THE EXPRESSION OF THE INTERFERON INDUCED ANTIVIRAL STATE. (E.) Tan, Y. H. (Kline Biol. Tower, Yale U., New Haven, Conn.), E. L. Schneider, J. Tischfield, C. J. Epstein and F. H. Ruddle. *Science* 186(4158):61-63, 1974.

Fibroblast cultures were established from skin biopsies of patients with Down's syndrome and from their normal siblings. To quantitatively assess the antiviral state induced by interferon in human trisomic 21 (T-21) and normal diploid (D-21) cells, five matched pairs of fibroblast cultures were exposed for 20-24 hr to different concentrations of human leukocyte interferon. The cells were subsequently challenged with vesicular stomatitis virus (VSV) and examined 36-48 hr later for virus-induced cytopathogenic effects (CPE). The concentrations of human interferon required to inhibit viral replication by 50% were 3-7 times higher for the D-21 than for the T-21 cells. The T-21 cells were more sensitive than the D-21 cells to the action of interferon; this effect was specific for trisomy of chromosome 21 since the concentration required to induce an antiviral state in T-18 and T-13 fibroblasts was the same as required for protection of D-21 fibroblasts. The T-21 cells were also 3-7 times more sensitive than the D-21 cells to the antiviral action of poly(I)·poly(C); this was not due to a nonspecific increase in interferon induction. The data suggest that the extra chromosome 21 in T-21 cells is re-

sponsible for the enhancement of protection by interferon, which is consistent with the assignment of the gene for the expression of the antiviral state to chromosome 21.

2914 ATTEMPTS TO DETECT DEOXYRIBONUCLEIC ACID FROM *AGROBACTERIUM TUMEFACIENS* AND BACTERIOPHAGE PS8 IN CROWN GALL TUMORS BY COMPLEMENTARY RIBONUCLEIC ACID/DEOXYRIBONUCLEIC ACID-FILTER HYBRIDIZATION. (E.) Eden, F. C. (Dept. Microbiol., U. Washington, Seattle), S. K. Farrand, J. W. Powell, A. J. Bendich, M. D. Chilton, E. W. Nester and M. P. Gordon. *J Bacteriol* 119(2):547-553, 1974.

Labeled RNA complementary to *Agrobacterium tumefaciens* DNA and PS8 bacteriophage DNA (cRNA) were used in a systematic study of the sensitivity of cRNA/DNA-filter hybridization for detection of small amounts of phage or bacterial DNA immobilized on filters. *A. tumefaciens* cRNA of specific activity 10^6 to 2×10^6 cpm/ μ g reacted to a significant extent when the DNA-filter contained 1% *A. tumefaciens* DNA in a salmon DNA background, but 0.1% *A. tumefaciens* DNA was not detectable. PS8 phage cRNA of the same specific activity reacted to a significant extent when the DNA-filter contained as little as 0.01% PS8 DNA in a salmon DNA background. Both kinds of cRNA were found to bind to tobacco crown gall tumor DNA-filters. Similar reaction was found with control normal callus DNA-filters but not with tobacco seedling DNA-filters. The "hybrids" formed by cRNA with normal callus and tumor DNA-filters had low thermal stability. No evidence was found for bacterial or phage DNA in crown gall tumor DNA.

2915 β -AMINOISOBUTYRIC ACID, A NEW PROBE FOR THE METABOLISM OF DNA AND RNA IN NORMAL AND TUMOROUS TISSUE. (E.) Nielsen, H. R. (Dept. Clin. Chem., Sundby Hosp. Copenhagen, Denmark), K.-E. Sjölin, K. Nyholm, B. S. Baliga, R. Wong and E. Borek. *Cancer Res* 34(6):1381-1384, 1974.

Female Holtzman rats were injected i.p. with a mixture of labeled L-methionine and formic acid. Four days later, all were injected i.p. with a homogenate of a 5-6 day old Novikoff hepatoma, after which they were again injected with the radioactive mixture. In a second experiment, Buffalo rats bearing Morris hepatomas were injected with the same radioactive mixture. One day after injection of the labeled mixture in the Holtzman rats, there was a massive urinary excretion of labeled newly synthesized β -aminoisobutyric acid (AIB). The amount excreted diminished greatly by the second day and continued to diminish at a much slower rate subsequently. A decrease in the daily excretion was particularly notable 6-7 days after tumor implantation, when the tumors were 1-15 g in size. The excretion of AIB by the Buffalo rats remained essentially constant, being similar to that in the normal animal. The 5-methylcytosine in the Novikoff hepatoma DNA was extensively labeled, as was the thymine in the tumor DNA; both were labeled *via* the radioactive methionine. Extensive labeling was also observed in the thymine of DNA extracted from regenerating liver

tissue; the labeling was not as high as in the tumor tissue.

- 2916 CONTENT OF SOME TRACE ELEMENTS IN SARCOMA M-1 DNA IN DYNAMICS OF MALIGNANT GROWTH. (E.) Andronikashvili, E. L. (Inst. Physics, Acad. Sci. Georgian SSR, Tblissi, USSR), L. M. Mosulishvili, A. I. Belokobilski, N. E. Kharabadze, T. K. Tevzieva and E. Y. Efremova. *Cancer Res* 34(2):271-274, 1974.

M-1 sarcomas were transplanted into albino rats, which were killed 10, 14, 18, or 26 days later. The zinc, iron, antimony, chromium, cobalt, and scandium levels in the tumor DNA at the time of death were determined by neutron activation analysis. The iron and chromium concentrations decreased until the 18th day, after which they increased, while the maximum antimony and scandium concentrations were observed on the 14th day. The zinc concentration varied only slightly throughout the course of the disease. The concentrations of all these elements were higher in Walker 256 carcinosarcoma DNA, and lower in normal liver tissue. The zinc concentration in the RNA from both tumor types and normal liver tissue was higher than in the DNA from these tissues, but the concentrations of most other metals were lower.

- 2917 PANCREATIC ISLET CELL TUMORS IN DOMESTIC ANIMALS. DATA FROM 11 COLLEGES OF VETERINARY MEDICINE IN THE UNITED STATES AND CANADA. (E.) Priester, W. A. (Nat'l. Cancer Inst., Bethesda, Md.). *J Nat'l Cancer Inst* 53(1):227-229, 1974.

Between 1964-1972, pancreatic islet cell tumors (ICTs) were reported in 27 dogs and 2 cats by 11 colleges of veterinary medicine in the United States and Canada. Estimated relative risk values for selected canine breeds showed a significant excess of ICTs only in standard poodles. Increasing age was associated with increasing risk, but there was no evidence of an age peak. Tumor occurrence in the 27 dogs was about equally divided by sex. In the dogs, 17 of the tumors were classified functionally active (all insulin-secreting), five were inactive, and five were not specified. In the cats, one tumor was classified active and the other inactive. One cat and three dogs had other primary tumors diagnosed before, with, or after the ICT, but these tumors were those expected in the older animals represented. Some of the features of the ICTs were remarkably similar to those reported in 52 humans with islet cell carcinoma.

- 2918 KERATOCANTHOMA AND MULTIPLE CARCINOMAS. (E.) Poleksic, S. (VA Ctr., Hampton, Va.). *Br J Dermatol* 91(4):461-463, 1974.

- 2919 A RECONSIDERATION OF THE BIOLOGY OF CARCINOMA OF THE PROSTATE. (E.) Williams, G. (Roy. Marsden Hosp., London, England), D. M. Wallace and H. J. G. Bloom. *Br J Urol* 46(1):61-64, 1974.

- 2920 TRAUMA AS A CAUSE OF BRAIN TUMOR: A MEDICOLEGAL DILEMMA. (E.) Dunsmore, R. H. (Hartford Hosp., Conn.) and M. Roberts. *Conn Med* 38(10):521-523, 1974.

- 2921 (³²P)PHOSPHORYL TRANSFER BY ENDOGENOUS PROTEIN KINASE AT THE GLIA AND GLIOMA CELL SURFACE IN CULTURE INTO EXTRINSIC ACCEPTOR PROTEINS. (E.) Agren, G. (Biomed. Ctr., Uppsala, Sweden) and G. Ronquist. *Acta Physiol Scand* 92(3):430-432, 1974.

- 2922 THE TRANSPORT OF SULFATE IONS ACROSS THE MEMBRANE OF THE EHRlich ASCITES TUMOR CELL. (E.) Levinson, C. (U. Texas Hlth. Sci. Ctr., San Antonio) and M. L. Villereal. *J Cell Physiol* 85(1):1-14, 1974.

- 2923 SUBACUTE MYELOMONOCYTIC LEUKEMIA. CLINICAL, MORPHOLOGIC AND ULTRASTRUCTURAL STUDIES OF 10 CASES. (E.) Sexauer, J. (Simpson Mem. Inst., U. Michigan, Ann Arbor), L. Kass and B. Schnitzer. *Am J Med* 57(6):853-861, 1974.

- 2924 HYALURONIC ACID SYNTHESIS IN A CELL-FREE SYSTEM FROM RAT FIBROSARCOMA. (E.) Hopwood, J. J. (Joseph P. Kennedy, Jr., Mental Retardation Res. Ctr., Chicago, Ill.), F. W. Fitch and A. Dorfman. *Biochem Biophys Res Comm* 61(2):583-590, 1974.

- 2925 PRIMARY SEQUENCE OF U-1 NUCLEAR RIBONUCLEIC ACID OF NOVIKOFF HEPATOMA ASCITES CELLS. (E.) Reddy, R. (Baylor Coll. Med., Houston, Tex.), T. S. Ro-Choi, D. Henning and H. Busch. *J Biol Chem* 249(20):6486-6494, 1974.

- 2926 TRANSCRIPTION OF RIBOSOMAL RNA PRECURSORS UNCHANGED DURING COMPENSATORY RENAL HYPERTROPHY. (E.) Hill, J. M. (Med. Coll. Georgia, Augusta). *Proc Am Assoc Cancer Res* 15(March):9, 1974.

- 2927 TRYPTOPHAN METABOLISM AND URINARY STEROIDS IN BREAST AND LUNG CANCER. (E.) Rose, D. P. (Div. Clin. Oncol., U. Wisconsin, Madison), Z. Randall, E. Bell and R. D. Bulbrook. *Proc Am Assoc Cancer Res* 15(March):16, 1974.

- 2928 SEPARATION AND CHARACTERIZATION OF DNA POLYMERASES IN HUMAN LEUKEMIC CELLS. (E.) Lewis, B. J. (Nat'l. Inst. Hlth., Bethesda, Md.), J. W. Abrell and R. C. Gallo. *Proc Am Assoc Cancer Res* 15(March):17, 1974.

- 2929 NONHISTONE CHROMATIN PROTEINS OF TRANSPLANTABLE RAT HEPATOMAS AND KIDNEY TUMORS. (E.) Reeck, G. R. (Nat'l. Inst. Hlth., Bethesda, Md.) and H. P. Morris. *Proc Am Assoc Cancer Res* 15(March):29, 1974.

- 2930 MELANOCYTE CONTACT-INHIBITORY FACTOR (MCIF): TRANSFER OF NORMAL *IN VITRO* GROWTH CONTROL TO HAMSTER MALIGNANT MELANOCYTES. (E.) Lipkin, G. (New York U. Sch. Med., N.Y.) and M. E. Knecht. *Proc Am Assoc Cancer Res* 15(March):61, 1974.
- 2931 RETENTION OF ORIGINAL HUMAN OVARIAN CANCER MARKERS AFTER CULTIVATION *IN VITRO*. (E.) Calascibetta, F. (Nassau Hosp., Mineola, N.Y.), G. Miroff and M. C. Li. *Proc Am Assoc Cancer Res* 15 (March):61, 1974.
- 2932 CELL-MEDIATED FACTORS THAT STIMULATE GROWTH OF HUMAN BREAST CARCINOMA CELLS IN TISSUE CULTURE. (E.) Lasfargues, E. Y. (Inst. Med. Res., Camden, N.J.), W. G. Coutinho and D. H. Moore. *Proc Am Assoc Cancer Res* 15(March):67, 1974.
- 2933 NUCLEOTIDE SEQUENCE AND INTRANUCLEAR LOCALIZATION OF NUCLEAR U1 RNA IN NOVIKOFF HEPATOMA ASCITES CELLS. (E.) Ro-Choi, T. S. (Baylor Coll. Med., Houston, Tex.), R. Reddy, N. B. Raj, D. Henning and H. Busch. *Proc Am Assoc Cancer Res* 15(March):85, 1974.
- 2934 QUANTITATIVE STUDIES ON THE NADH AND NADPH MICROSOMAL ELECTRON TRANSPORT CHAINS OF MORRIS HEPATOMAS WITH VARYING GROWTH RATES. (E.) Zimmerman, J. J. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and C. B. Kasper. *Proc Am Assoc Cancer Res* 15(March):88, 1974.
- 2935 CELL PROLIFERATION: ALTERATION IN THE NUMBER OF BINDING SITES FOR RNA POLYMERASE IN CHROMATIN OF WI-38 FIBROBLASTS STIMULATED TO PROLIFERATE BY A NUTRITIONAL CHANGE. (E.) Hill, B. T. (Temple U. Sch. Med., Philadelphia, Pa.) and R. Baserga. *Proc Am Assoc Cancer Res* 15(March):31, 1974.
- 2936 METASTATIC INCIDENCE OF A SPONTANEOUS MURINE BREAST TUMOR. (E.) Fugmann, R. A. (Catholic Med. Ctr., Woodhaven, N.Y.), R. L. Stolfi, J. C. Anderson and D. S. Martin. *Proc Am Assoc Cancer Res* 15(March):37, 1974.
- 2937 MODIFICATION OF ACTH CONTROL IN ADRENOCORTICAL CARCINOMA CELLS. (E.) Ahmed, N. K. (U. Tennessee Med. Units, Memphis), L. S. Sutliff and R. K. Sharma. *Proc Am Assoc Cancer Res* 15(March):41, 1974.
- 2938 POTENTIATION OF EXTRAHEPATIC MORRIS HEPATOMA GROWTH BY DIVERSION OF PORTAL VENOUS BLOOD FROM THE LIVER. (E.) Reichle, R. M. (Temple U. Health Sci. Ctr., Philadelphia, Pa.), H. P. Morris and F. A. Reichle. *Proc Am Assoc Cancer Res* 15(March):92, 1974.
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- 2940 TYROSINASE FROM MELANOSOMES OF HUMAN MELANOMA. (E.) Nishioka, K. (M. D. Anderson Hosp., Houston, Tex.) and M. M. Romsdahl. *Proc Am Assoc Cancer Res* 15(March):58, 1974.
- 2941 TUMOR INVASION INTO THE DIAPHRAGM: A SCANNING ELECTRON MICROSCOPIC ANALYSIS. (E.) Strauli, P. (Cancer Res. Div., Zurich, Switzerland). *Experientia* 30(6):710, 1974.
- 2942 WHEN IS REPLICATIVE DNA SYNTHESIS INITIATED IN REGENERATING RAT LIVER? (E.) Kizer, D. E. (Noble Fdn., Inc., Ardmore, Okla.) and B. A. Howell. *Proc Am Assoc Cancer Res* 15(March):108, 1974.
- 2943 RECOGNITION OF A NEW DNA POLYMERASE IN MOUSE LIVER: MAMMALIAN DNA POLYMERASE III. (E.) Matsukage, A. (Nat'l. Inst. Hlth., Bethesda, Md.), E. Bohn and S. H. Wilson. *Proc Am Assoc Cancer Res* 15(March):129, 1974.
- 2944 CYCLIC NUCLEOTIDE PHOSPHODIESTERASE (cPDE) IN METASTASIZING AND NON-METASTASIZING RAT MAMMARY CARCINOMAS (MT). (E.) Chatterjee, S. (Roswell Park Mem. Inst., Buffalo, N.Y.) and U. Kim. *Proc Am Assoc Cancer Res* 15(March):130, 1974.
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CARCINOGENESIS ABSTRACTS

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CARCINOGENESIS ABSTRACTS

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N O T I C E

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PREFACE

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NOTE

Journal names are abbreviated according to the list of abbreviations used by *Index Medicus*. For journals not covered by *Index Medicus*, the abbreviations (with some modifications) found in *World Medical Periodicals*, 3rd Edition, are used.

LANGUAGE ABBREVIATIONS

Afr.	Afrikaans	It.	Italian
Ar.	Arabic	Jap.	Japanese
Bul.	Bulgarian	Kor.	Korean
Ch.	Chinese	Latv.	Latvian
Cz.	Czech	Lith.	Lithuanian
Dan.	Danish	Nor.	Norwegian
Dut.	Dutch	Pol.	Polish
E.	English	Por.	Portuguese
Eston.	Estonian	Rum.	Rumanian
Fin.	Finnish	Rus.	Russian
Fl.	Flemish	Ser.	Serbo-Croatian
Fr.	French	Sl.	Slovak
Ger.	German	Sp.	Spanish
Gr.	Greek	Sw.	Swedish
Heb.	Hebrew	Th.	Thai
Hun.	Hungarian	Turk.	Turkish
Ic.	Icelandic	Uk.	Ukrainian
ln.	Indonesian	Viet.	Vietnamese

ABBREVIATIONS USED IN ABSTRACTS

ACTH	adrenocorticotrophic hormone	mg	milligram(s)
ADP	adenosine diphosphate	min	minute(s)
AMP	adenosine monophosphate	ml	milliliter(s)
ATP	adenosine triphosphate	mm	millimeter(s)
C	degrees centigrade	MTD	maximum tolerated dose
cm	centimeter(s)	ng	nanogram (10^{-9})
CNS	central nervous system	pg	picogram (10^{-12})
cpm	counts per minute	p.o.	orally
DNA	deoxyribonucleic acid	ppm	parts per million
e.g.	for example	r	Roentgen
g	gram(s)	RBC	red blood cells (erythrocytes), red blood count
µg	microgram(s)	resp.	respectively
hr	hour(s)	RNA	ribonucleic acid
i.m.	intramuscular	s.c.	subcutaneous
i.p.	intraperitoneal	sec	second(s)
IU	international unit(s)	U	unit(s)
i.v.	intravenous	UV	ultraviolet
kg	kilogram(s)	WBC	white blood cells (leukocytes), white blood count
LD ₅₀	median lethal dose(s)		
m	meter(s)		
M	molar	wk	week(s)
mEq	milliequivalent(s)	wt	weight(s)
mM	millimolar	yr	year(s)
µM	micromolar		
mC, µC	milli-,microcurie(s)		

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- 3001 MECHANISMS INVOLVED IN ONCOGENESIS. (Ger.) Grundmann, E. (Pathol. Inst., U. Munster, Germany). *Verhandl Dtsch Ges Inn Med* 78:34-45, 1972.

Cellular transformation as a primary process in oncogenesis is due to the metabolized "terminal" (ultimate carcinogen) form rather than to the primary form of the carcinogen. Such "ultimate" carcinogens may attack the DNA in the cell nucleus directly, but recent studies suggest that primary reaction with RNA, or binding with cytoplasmatic proteins, is more likely. Deletion of an enzyme or enzyme group, or induction of an abnormal enzyme, are equally possible. Carcinogenic DNA virus is able to incorporate its DNA into cellular DNA either indirectly or directly, while carcinogenic RNA virus polymerizes a DNA that is complementary to its RNA and incorporates viral RNA information in the nucleus by means of "reverse transcriptase". Carcinogens react very actively with transfer-RNA. Transfer-RNA-methylase plays a dominant role in this process. Widespread carcinogenic virus-RNAs can be stimulated to replicate by chemical carcinogens so that malignant transformation is induced. Transformation or subsequent tumor growth can be stimulated or inhibited by primarily extracellular but endogenous factors, such as hormones. Transformed cells may assume new antigenic properties which make them "foreign" to the body. The organ-specific action of chemical carcinogens is apparently related to their metabolic conversion to ultimate carcinogens in specific organs. (45 references)

- 3002 THE FUNCTION AND MECHANISM OF PROMOTERS OF CARCINOGENESIS. (E.) Boutwell, R. K. (Med. Ctr., U. Wisconsin, Madison). *CRC Crit Rev Toxicol* 2(4):419-444, 1974.

Recent progress in understanding the function and mechanism of promoters of carcinogenesis is reviewed. Tumor formation in mouse epidermis has been an excellent model for studying carcinogenesis. Promoters of carcinogenesis are discussed in terms of historical background, the chemical nature of promoters, and the biological function of promoters. Gene activation as the mechanism of promoters is considered with regard to morphological considerations, receptor sites and the role played by the cell membrane and possible intracellular receptors, histone metabolism, RNA synthesis, and protein synthesis. The data indicate that the essential mechanism of a promoter is gene activation. Two components are involved in the promoting process: a converting stimulus which transforms the initiated cell into a dormant tumor cell; and a propagating component, which stimulates cell division by gene activation. Alternative mechanisms are discussed in terms of DNA repair inhibition, depressed immunological reactivity of the host, and other less well-substantiated mechanisms. There is a need for rapid, highly predictable assays for carcinogenicity. The stimulated synthesis of lecithin may be a suitable means for the detection and assay of environmental

tumor-promoting agents. Other consequences of promoter treatment, including RNA and protein synthesis, should also be explored. (157 references)

- 3003 LIVER TUMORS AND THE PILL. (E.) Anonymous. *Br Med J* 3(5922):3-4, 1974.

A definite cause-and-effect relation has yet to be established between hepatic neoplasia and the use of oral contraceptives. In the past 5 yr, 14 cases of benign hepatic adenomata have been reported among women using these drugs. Of these 14, 13 had been taking oral contraceptives for at least 2 yr, usually longer, but one developed symptoms after only 6 months. Information on benign hepatic adenomata suggests it is an exceedingly rare disease, so that these 14 cases collected over such a short period suggests a striking increase in incidence. The lesions are histologically benign and well demarcated from surrounding liver tissue. Bile duct reduplication was prominent in at least 3 cases. Most of the tumors were markedly vascular with small dilated blood vessels. Because of their vascularity these tumors are very apt to bleed. Of the reported cases, 9 presented with acute abdominal pain and shock from bleeding. Of these 9, 4 died. Elective resection is suggested due to the high incidence of life-threatening hemorrhage. The long-term use of oral contraceptives among healthy asymptomatic women has produced ultrastructural changes in the hepatocytes with hypertrophy of the smooth endoplasmic reticulum and mitochondrial abnormalities. Enzymes which metabolize foreign compounds in the body are situated on the smooth endoplasmic reticulum and thus such changes may be significant. Enzyme induction may potentiate the carcinogenicity of certain compounds, perhaps by increasing their conversion to toxic metabolites. (17 references)

- 3004 MAMMALS, MOSSES AND MNU. (E.) Anonymous. *Food Cosmet Toxicol* 12(1):147-153, 1974.

Recent data has linked carcinogenesis by *N*-nitroso compounds with the alkylation of nuclear DNA and RNA. *N*-7 alkylation may be of less importance than 0-6 alkylation as a critical factor in malignant transformation. It is likely that in the genesis of tumor cells, cytoplasmic mutations are at least as important as nuclear mutations, although there is no direct evidence concerning the genetic function of mitochondrial DNA. Since both methylnitrosourea (MNU) and its ethyl analogue (ENU) have short half-lives in aqueous solution, the rate of mutagenesis by these compounds appears to depend on the time during which the mutagens are allowed to act on the genetic material, and thus on the decay rate; the latter hinges on the pH, which is directly related to the mutagenicity of various nitrosoureas. Mosses offer several advantages for mutagenicity testing by their relative simplicity. In one

species, *Pogonatum aloides*, MNU was more toxic than ENU and caused more chromosomal damage at anaphase, but ENU induced a significantly higher mutation rate and a different spectrum of mutations. Early cytopathological changes noted after nitrosourea treatment include a striking accumulation of masses of glycogen in some cells (glycogenosis) and an increase in nuclear size. The evidence emphasizes the difficulty of establishing a firm connection between chemical interaction with nucleic acids and mutagenesis and carcinogenesis. Whereas chemical interaction takes place within min, several days may pass before a mutation is expressed and an even longer period elapses before tumors appear; secondary factors may operate during the interim period. (16 references)

- 3005 SAFETY MARGIN PROVIDED BY CURRENT STANDARDS FOR PROTECTION AGAINST IONIZING RADIATION. (Fr.) Bertin, M. (No affiliation). *Pollution Atmosphérique* 16(62):151-160, 1974.

Natural and artificial sources of ionizing radiation are listed and doses to which the general population and occupationally exposed persons are subjected are presented with respect to threshold doses of such radiation. The individual radiation dose due to natural radioactivity, amounting to 120 mrem/yr in France, is about of the same order of magnitude as the dose due to therapeutic and diagnostic irradiation. Individual irradiation due to radioactive fallout from A-bomb explosions amounts to 2 mrem/yr, corresponding to a genetically significant dose of 80 mrem. The irradiation outside nuclear power plants is too low to be measurable and is not expected to exceed 1 mrem/yr for the next 20 yr. The radiation dose in occupational exposure in the USA is estimated at about 1 mrem/yr for the entire population. Current standards are set at or below 1.5 rem/yr, depending on the type of exposure, and the genetically significant dose is set at 5 rem in 30 yr. These standards provide for a substantial safety margin due to the well-established lack of proportionality in the dose-effect relationship, and in view of the experimentally established, high threshold doses for the major effects of radiation, e.g., cataract, decreased longevity, skin and bone cancers, leukemia, and teratogenesis. No skin cancer was observed following irradiation at doses below 1,500 rem. No bone cancer was found in female workers exposed to ^{226}Ra in fluorescent paint when the dose accumulated in the skeleton was below 10,000 rem. Bone cancer was induced in dogs and rats by injection of ^{90}Sr in doses larger than 30,000 rem and 35,000 rem, resp. The threshold dose for ^{224}Ra and ^{239}Pu with respect to bone cancer may be on the order of magnitude of 100-200 rad. The threshold dose for leukemia was around 100 rem in Nagasaki survivors, while among Hiroshima survivors exposed primarily to neutrons, the incidence of leukemia decreased with decreasing dose. (No references)

- 3006 HERPESVIRUSES, LATENCY AND CANCER: A BIOCHEMICAL APPROACH. (E.) Roizman, B. (Dept. Microbiol., U. Chicago, Ill.). *J Reticuloendothel Soc* 15(4):312-321, 1974.

Many species, including man, can be infected by more than one of the herpesviruses, but the topology of the infected cells in the body does not always overlap. Also, although herpesviruses always destroy the cells in which they multiply, these viruses are able to survive in the host without causing clinically obvious disease; this phenomenon is known as latency. Herpesviruses are oncogenic in a number of experimental animals and have been implicated in human cancer. Does the ability to cause latent infections play a major role in human cancer? Neither latency nor cancer can be accounted for on the basis of current knowledge of productive infection. However, the analysis of productive infections does point a way to the elucidation of latency and cancer. If a virus is to coexist with its host, a defined level of molecular interaction between host and viral gene products must exist. Thus, both the biochemical basis of latency and the etiologic role of herpesvirus in human cancer may emerge from broad analyses of these interactions at the molecular level. (42 references)

- 3007 BIOCHEMICAL APPROACHES TO DETECTION OF HERPES SIMPLEX VIRUS TYPE 2 IN CERVICAL CARCINOMA. (E.) Goodheart, C. R. (BioLabs, Inc., Northbrook, Ill.). *Cancer Res* 34(5):1136-1139, 1974.

Nucleic acid hybridization techniques are highly sensitive methods for determining the presence of herpes simplex type 2 genomes in cervical cancers. Measurement of the rate of reassociation between labeled, purified viral DNA and DNA extracted from the tumor cells may be necessary to achieve adequate sensitivity if only a portion of the viral genome is present and if tumors contain substantial proportions of cells other than tumor cells. A large number of cervical tumors in various stages, as well as many control tissues, need to be studied to evaluate the role of herpes virus type 2 in the etiology of cervical carcinoma. (28 references)

- 3008 ROUS SARCOMA VIRUS: A NEW ROLE FOR TRANSFER RNA. (E.) Maugh, T. H., II (No affiliation). *Science* 186(4158):41, 1974.

The Rous sarcoma virus appears to use a cellular transfer RNA as a primer for its own RNA-directed DNA polymerase. This is the first naturally occurring primer to be identified. It is the last polynucleotide dissociated from the viral genome of particles grown in chick embryo cells as the temperature is slowly raised up to 69 C; the template primer activity is halted when it becomes dissociated. Labeled nucleotides used as substrates for the reverse trans-

criptase become covalently bonded to the suspected primer. The primer molecule contains four sets of homologous sequences which are bonded by Watson-Crick base pairing to fold the molecule into the cloverleaf shape characteristic of transfer RNAs. The anticodon C_mCA was observed at the appropriate site on the folded polynucleotide. When tested under conditions for linking transfer RNAs to amino acids, the primer could accept only tryptophan. The primer produces a characteristic pattern of oligonucleotides when digested with the enzyme ribonuclease T1 and subjected to 2-dimensional paper electrophoresis. Polynucleotides with identical sequences have been found in chicken and other avian cells, rat cells, and human cells. It is likely that these polynucleotides are the tryptophan-specific transfer RNAs used by the cells. (No references)

3009 THE PROBLEMS RAISED BY THE SEARCH FOR MORPHOLOGICAL EVIDENCE IN FAVOUR OF THE ROLE OF VIRUSES IN HUMAN CANCER. (E.) Haguenau, F. (Lab. Exp. Med., Coll. France, Paris). *Proc Fifth Int Symp Biol Characterization Hum Tumors, Bologna, April 4-6, 1973* p. 66-79.

Most known viruses can be recognized under the electron microscope. However, results of examining human tumors for viruses vary according to whether biopsies, tumor extracts, diverse fluids, or tissue cultures are used. Negative results with biopsies can be explained either on the assumption that the virus is present in the cell in a masked state, or that the amount is too small to be detected in 300 Å thick sections. The negative contrast method, which is applied mainly to tissue extracts or biological fluids, eliminated the quantitative aspect of the problem but is associated with the artificial formation of virus-like particles from cellular debris. With refinements in purification techniques and methods for electron microscopy examination of specimens, findings appear more reliable. Results for virus particles in human milk samples are important though inconclusive. Examination of tissue culture material represents the greatest asset in the search for human tumor viruses. A number of human cancer cell lines grown *in vitro* have been shown to contain viruses belonging to the oncornavirus or herpes groups. However, most workers have underestimated the risk of contamination of a culture by mycoplasma, unrelated viruses, or even unrelated strains of cells. Supplementary studies in immunology, biochemistry, and genetics will be necessary to demonstrate a host/virus relation that transcends simple association. (72 references).

3010 BIOCHEMICAL FACTORS INVOLVED IN THE CELLULAR DETACHMENT FROM TUMORS. (E.) Sylven, B. (Karolinska Hosp., Stockholm, Sweden). *Schweiz Med Wochenschr* 104(8):258-261, 1974.

The knowledge on the biochemical composition of interstitial fluid of solid transplanted mouse tumors is summarized. Specific changes in the composition

of tumor interstitial fluid (IF) as compared with that of normal tissues may be important in explaining the abnormal behavior of tumor cells. The original IF is locally modified by tumor and host products, these topical additions varying in different tumors and tumor regions. The protein content of the peripheral tumor IF is twice the normal figure, the protein content of central tumor IF being even higher. Compared with normal lymph or IF, tumor IF is characterized by a large addition of lysosomal and cytoplasmic enzymes. The lysosomal proteinase cathepsin B is of special interest. The haptoglobin concentration is also raised in ascites tumor fluid and probably in solid tumor IF and the blood plasma of tumor-bearing mice; the haptoglobins are powerful physiological cathepsin B inhibitors. The ionic milieu of free tumor IF is much the same as that of normal plasma. The acid-base composition indicates an acid shift, depending on the degree of glycolysis, which would hamper the ameboid movement of cells. In addition, the glucose concentration of solid tumor IF is decreased, especially in central necrotic zones. Evidence indicates that cathepsin B is available at some tumor cell surfaces and that it is leaking out into the IF; this enzyme in an active state is capable of cellular disaggregation. Chemical assays further suggest an early release of a sialopeptide from the cell surfaces. In general, it must be concluded that tumor cells present a deranged permeability. (34 references)

3011 MOLECULAR PATHOLOGY OF THE CANCER CELL. (E.) Paul, J. (Beatson Inst. Cancer Res., Glasgow, Scotland) and I. Hickey. *J Clin Pathol [Suppl]* 27(7):4-10, 1974.

The lesions which result in the formation of a cancer cell are very often, and possibly invariably, associated with abnormalities of nucleic acid and/or protein synthesis. During the development of some tumors, e.g., hepatomas, specific enzyme activities are lost. It is also common for cancer cells to synthesize proteins such as they might be expected to produce on the basis of the presumed tissue of origin. Lesions in the metabolic machinery of the cell which could give rise to disturbed patterns of protein synthesis might occur during the replication of DNA, as a result of mutation or the insertion of the viral DNA, or during the transcription of DNA into RNA. The kinds of RNA present in cancer cells are often different from the kinds of RNA in normal cells, and a few studies have shown that the pattern of transcription from chromatin from tumor cells differs from that of normal cells. Probably all RNA tumor viruses contain reverse transcriptase, which fact has led to several hypotheses of carcinogenesis based on the implication that RNA tumor viruses could be transcribed into DNA which, in turn, could be integrated into the host genome. It seems probable that in cancer there are specific molecular lesions which produce interference with normal control circuits; in viral carcinogenesis, viral and host information may interact intimately. When an erythroleukemic mouse cell line produced by the Friend virus is treated with dimethylsulfoxide, a portion of the cell population synthesizes hemo-

globin. Results of genetic studies involving lines of these cells which do and do not induce hemoglobin suggest that the Friend virus produces a signal which is in some way involved in the regulation of hemoglobin synthesis. This might indicate a close relationship between tumor viruses and host cells. (29 references)

- 3012 FSA - FOETAL SULPHOGLYCOPROTEIN ANTIGEN ASSOCIATED WITH GASTRIC CANCER. (E.) Hakkinen, I. P. T. (Dept. Path., U. Turku, Finland). *Transplant Rev* 20:61-76, 1974.

In this review the main emphasis is on studies concerning the use of gastric fetal sulfoglycoprotein antigen (FSA) as a diagnostic tool for early detection of gastric malignancy. An attempt is also made to discuss the relationship between the appearance of FSA in the gastric juice and the development of gastric cancer or future tendency to develop gastric cancer. Separation methods for FSA are described, its physicochemical properties discussed, and its immunochemical characterization presented in some detail. Studies of FSA in the Finnish population are reported, including the method for obtaining the required sample of gastric juice. In one of these studies 78 patients suffering from a histologically verified gastric cancer were examined for FSA in gastric juice, and the antigen was present in 97% of the cases. (22 references)

- 3013 PRELEUKEMIC STATES. (E.) Pierre, R. V. (Mayo Clin., Rochester, Minn.). *Semin Hematol* 11(1):73-92, 1974.

Disorders which are associated with a high risk of leukemia include sex chromosomal abnormalities such as Klinefelter's syndrome, Fanconi's anemia, Bloom's syndrome, ataxia telangiectasia, Kostmann's disease, radiation exposure, and exposure to drugs or chemicals such as benzene and phenylbutazone. Various hematologic changes have also been noted in potentially leukemic or preleukemic patients: aplastic anemia, pure red cell aplasia, thrombocytopenia, neuropenia, refractory sideroblastic anemia, macrocytic anemia, and monocytosis. A prospective study of patients with suspected preleukemia was begun in 1967 to determine whether direct bone marrow chromosome studies are clinically useful in recognizing the preleukemic states. Chromosome studies were first conducted using 103 control subjects (62 males and 41 females) with no disorder known to produce chromosome abnormalities. Direct bone marrow studies showed abnormalities in 55 of 105 patients with overt acute nonlymphocytic leukemia and 72 of 233 patients (131 males and 102 females) with suspected preleukemia. The data suggest that the incidence and type of cytogenetic abnormalities in preleukemic subjects in whom acute leukemia has developed are no different from those observed in patients with overt leukemia. A combination of clinical features, ancillary laboratory data, cytogenetic studies, and data from bone marrow cell cultures may permit the accurate recognition of preleukemic states in the near future. (207 references)

- 3014 PRECANCEROUS LESIONS AND THEIR DETECTION AND DIAGNOSIS. (E.) Kloss, L. G. (No affiliation). *Recent Results Cancer Res* 44:47-52, 1974.

A brief summary of the accomplishments of cytology within the realm of early cancer detection is presented. The usage of cytology in the detection and diagnosis of precancerous lesions of the cervix has received wide popular support; the same does not apply to other organs, although sophisticated observers may achieve diagnostic results for other organs that closely match those recorded for the uterine cervix. Good results of cytologic diagnosis of the endometrium have been achieved with endocervical aspirations. Nonpapillary carcinoma of the urinary bladder recently received full recognition as a result of cytologic screening and follow-up studies of industrial workers exposed to potent bladder carcinogens. Eighty percent of lung cancers can be accurately diagnosed by cytologic examination of the sputum, and cytologic examination of scrapings of all lesions of buccal cavity contributed substantially to the identification of carcinoma *in situ* except in situations where the lesions were heavily keratinized. (29 references)

- 3015 HODGKIN'S DISEASE 1974. (E.) Wiernik, P. H. (Natl. Cancer Inst., Baltimore Cancer Res. Ctr., Md.). *Johns Hopkins Med J* 135(1):25-32, 1974.

This review briefly outlines the recent laboratory and clinical advances in the understanding and management of Hodgkin's disease. With regard to the etiology and pathogenesis of Hodgkin's disease, significant elevations in the mean anti-Epstein-Barr virus titers have been found in the sera of Hodgkin's disease patients. Two tumor-associated antigens have been found in splenic nodules of Hodgkin's disease, but not in surrounding normal spleen tissue. Clinical cure may represent a state of equilibrium in which the host has come to terms with his disease; the mechanism of this equilibrium is being studied *in vitro*. W-5 tissue antigen has been found in significant excess in Hodgkin's disease patients, and HL-A-5 occurs less frequently than expected in Hodgkin's disease. Diagnostically, recent research has possibly linked increased malignant lymphoma with heroin addiction. Recent epidemiological data suggest that Hodgkin's disease may be transmitted horizontally through social interaction. Both tonsillectomized and appendectomized patients have an increased risk of Hodgkin's disease. There is conflicting evidence regarding the hypothesis that Hodgkin's disease represents two diseases: an infectious disease of young adults, and a neoplastic disease of older people. The controversy over laparotomy as a staging device continues, and ⁵⁷Co-labeled bleomycin appears to be ideally suited as a scanning agent. Splenic involvement may always mean disseminated extranodal disease. Combination chemotherapy is probably superior to single agent chemotherapy for patients with advanced Hodgkin's disease. New therapeutic drugs under investigation in-

clude bleomycin, streptozotocin, and the nitrosoureas, especially CCNU. With regard to prognosis, splenic invasion appears to be an indication of an unfavorable prognosis. (57 references)

3016 NASOPHARYNGEAL CARCINOMA: RECENT STUDIES AND OUTLOOK FOR A VIRAL ETIOLOGY. (E.)

de-The, G. (Intl. Agency Res. Cancer, Lyon, France) and A. Geser. *Cancer Res* 34(5):1196-1206, 1974.

Recent studies of the role of the lymphotropic Epstein-Barr virus in the development of nasopharyngeal carcinoma (NPC) are reviewed. In electron microscopy, close contacts were noted between lymphoid and epithelial cells in the normal nasopharyngeal mucosa, in NPC biopsies, and in the *in vitro* growths derived from the NPC biopsies. Such close contacts with occasional loss of adjacent cell membrane continuity suggest that cell cooperation might play an important role in NPC development if a lymphotropic virus is involved. In serology, it was observed that NPC sera exhibited 10-fold higher antibody titers than Burkitt's lymphoma sera against a soluble complement-fixing (CF) antigen. CF antibody titers were very high and stable in NPC patients regardless of the stage of the disease and of the clinical evolution. CF antibodies did not appear to be related to viral capsid or early antigen activities. An ongoing seroepidemiological program, although not completed, shows that adult Chinese males have lower viral capsid antigen antibody titers and higher CF antibody titers (against a soluble antigen) than Indian males. Etiological hypotheses and research priorities are presented. (64 references)

3017 CANCER OF THE GASTROINTESTINAL TRACT:

EPIDEMIOLOGICAL ASPECTS. (E.) Macdonald, E. J. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.). *JAMA* 228(7):884-886, 1974.

The extreme high and low incidence rates of gastric cancer throughout the world predicate environmental factors as causative agents. Mortality rates from gastric cancer vary from state to state within the United States, nonwhites having higher rates than whites and men having higher rates than women. The rates also vary from country to country; they are extremely high in the Miyagi Prefecture in Japan, the middle provinces in Chile, among the blacks of Cape Province and South Africa, and in Finland, Iceland, Columbia, Yugoslavia, Hungary, and Poland, and low among Latins in five regions of Texas. In some countries, but not others, gastric cancer incidence increases with economic status. A familial history of gastric cancer is relatively high among gastric cancer patients. Nutrition is a prime suspect as a causative factor. The incidence of stomach cancer seems to vary inversely with the amount of corn in the diet, and to increase with exposure to phenol, talc, salt and nitrosamines. An antivitamin A factor in reheated foods may contribute to the induction of gastric cancer. (17 references)

3018 NASOPHARYNGEAL CARCINOMA: PRESENT STATUS OF KNOWLEDGE. (E.) Henderson, B. E. (U. Southern California Sch. Med., Los Angeles). *Cancer Res* 34(5):1187-1188, 1974.

The possible role of genetic factors in the etiology of nasopharyngeal carcinoma (NPC) is indicated by the fact that a relatively high rate of NPC is found among the Southern Chinese, a lower rate is present among Chinese from the more northern provinces, and the disease is relatively rare in Japan and India. The greater the admixture of Chinese blood in an ethnic group, the more likely it is that the NPC incidence rates will be elevated. Although NPC rates remain high in Chinese who immigrate to California, successive generations of Chinese born in the United States appear to be at decreasing risk. An increased frequency of the histocompatibility antigen HL-A2 may be a marker of genetic susceptibility to NPC in the Chinese population. Most environmental variables which have been suggested to play a role in the etiology of NPC have not been shown to be linked with increased risk of the disease. However, virtually 100% of NPC cases have elevated antibody titers to Epstein-Barr virus (EBV) regardless of the racial or geographical location of the cases. Whether EBV is a necessary cofactor for the development of NPC or a "passenger" virus remains unsolved. Although additional epidemiological evidence and age curve data indicate that some environmental factor is involved in the etiology of NPC, additional research is needed to confirm this hypothesis. Studies among populations with a lower rate of NPC are suggested. (27 references)

3019 THE ROLE OF GENETICS IN HUMAN CANCER. (E.)

Anderson, D. E. (M.D. Anderson Hosp. Tumor Inst., Houston, Tex.). *Cancer J Clin* 24(3):130-136, 1974.

Although definitive evidence of a genetic component in human cancer is not available, inheritable cancers are known to occur at virtually every major cancer site and organ category of man. The two-step mutation model for childhood cancer holds that cancer is caused by two mutational events, the first occurring either in a germ cell (hereditary) or a somatic cell (nonhereditary), and the second always occurring in a somatic cell. The model predicts that, compared with nonhereditary tumor, hereditary tumors will occur at an earlier average age; also, hereditary tumors will tend to be multiple, while the nonhereditary type will tend to be single. These predictions have been borne out in a variety of childhood and adult tumors, including Wilms' tumor, retinoblastoma, neuroblastoma, pheochromocytoma, basal cell carcinoma, medullary thyroid carcinoma, and hereditary adenocarcinomatosis. The model may also apply to some of the common cancers; the heritable forms, particularly in cases of breast cancer and colon cancer, may be more frequent than is generally suspected. In general, the genetic defect in the various inheritable cancers remains an unsolved question. Since the majority of inheritable cancers are dominantly inherited, early detection and genetic counseling is important. A detection program

for individuals with family histories of common neoplasms is feasible and will probably result in the detection of tumors at an earlier and more easily treated stage than is possible when detection is based on signs and symptoms. (20 references)

- 3020 THE GENETIC CONTROL OF LEUKEMOGENESIS. I. GENETIC SYSTEMS INVOLVED AT THE LEVEL OF VIRUS-CELL INTERACTION. (E.) Gisselbrecht, S. (Hosp. St.-Louis, Paris, France) and J. P. Levy. *Biomedicine* 20(2):95-101, 1974.

At least three mechanisms for the genetic control of virus-induced leukemogenesis can be proposed: control at the level of interaction between the virus and the cell target; control of the immune response directed against the virus or the antigenic transformed cells; and hematologic control of the availability of target hemopoietic cells and/or the multiplication of the leukemic cells. The genetic control of virus infection can theoretically be placed at various stages in the virus-cell relationship: exogenous virus penetration into the cell; replication of this virus by the cellular machinery, existence of an endogenic information for virus synthesis and/or expression; and malignant transformation of the cell by the viral genome. In both mice and chickens, a genetic control of the virus-cell relationship exists and occurs simultaneously at two levels. The induction of endogenic oncornaviruses is controlled by several genes, some of which are probably integrated virus genomes; the others could be regulatory genes which determine the inducibility of the viral genomes. The multiplication of exogenic as well as endogenic viruses can amplify the effect of the first system. It is controlled by other simple genetic systems which are also involved when leukemia viruses are artificially inoculated into host cells. These systems intervene in the chicken at the level of the virus-cell membrane interaction by directing the presence of specific virus receptors. In the mouse, they may act at the level of the intracellular virus replication. (53 references)

- 3021 SPONTANEOUS TUMORS OF THE NERVOUS SYSTEM IN ALBINO RATS. (E.) Fitzgerald, J. E. (Parke, Davis and Co., Ann Arbor, Mich.), J. L. Schardein and S. M. Kurtz. *J Natl Cancer Inst* 52(1):265-273, 1974.

A retrospective review of necropsies of 7803 Sprague-Dawley albino rats revealed 34 tumors originating in the brain or meninges for an overall incidence of 0.44%. In addition, four tumors of ganglion cell origin were found. The most frequent brain tumor was the astrocytoma (22). Other tumor types included oligodendroglioma (3), ependymoma (4), meningioma (3), ganglioneuroma (4) and optic nerve glioma (2). The tumors had a predilection for male rats and had a median latent period of between 17-18 months. (11 references)

- 3022 THE GENETIC CONTROL OF LEUKEMOGENESIS. II. GENETIC SYSTEMS INVOLVED IN THE CONTROL OF LEUKEMOGENESIS AS THEY ARE DETECTED *IN VIVO*. (E.) Gisselbrecht, S. (Hosp. Cochin, Paris, France) and J. P. Levy. *Biomedicine* 20(3):171-178, 1974.

The *in vivo* genetic control of virus-induced leukemia is reviewed. Resistance or sensitivity to the virus-induced leukemias is controlled by complex genetic systems involving several different genes acting at different levels of the host-virus relationship: the existence of information for endogenous type C viruses; control of the expression of this information; control of virus multiplication by governing the penetration into noninfected cells or by the repression of intracellular multiplication; the availability of target cells capable of virus transformation; control of the anti-virus or anti-tumor immune response. The optimal conditions for the expression of the phenotype "leukemia" are probably rarely presented. In man, if such a situation exists, it would probably be extremely difficult to demonstrate because of lacking prerequisites. New methods are needed to solve this problem, the study of families with a high incidence of leukemia possibly being the only way to approach the genetic control of leukemia in man. (61 references)

- 3023 ALPHA-FETOPROTEIN: IMMUNOCHEMICAL PURIFICATION AND CHEMICAL PROPERTIES. EXPRESSION IN NORMAL STATE AND IN MALIGNANT AND NON-MALIGNANT LIVER DISEASE. (E.) Ruoslahti, E. (Dept. Serol. Bacteriol., U. Helsinki, Finland), H. Pihko and M. Seppala. *Transplant Rev* 20:38-60, 1974.

This review is concerned with the isolation and purification of alpha fetoprotein (AFP) and summarizes results of the application of radioimmunoassays on the expression of AFP in normal and human disease processes and experimental liver disease in animals. AFP was purified from human fetuses and sera of hepatoma patients using immunoprecipitates as intermediates. Purification was also achieved using anti-AFP conjugated covalently to agarose. The physical and chemical characteristics of AFP were found to resemble those of albumin. Unlike albumin, human AFP is a glycoprotein containing about 4% carbohydrate. Human fetal and hepatoma AFP were indistinguishable antigenically, electrophoretically and with respect to amino acid composition, sugar composition and peptide maps. A radioimmunoassay based on the double antibody principle (RIA) was developed for human and mouse AFP. Using this method, small amounts of AFP were demonstrated in normal human serum suggesting that repression of the AFP gene(s) is not complete in adults. With RIA pathological AFP values were detected in many cases of human liver disease but some patients (15-20%) had a normal AFP level. In mice suffering liver damage induced by the administration of carbon tetrachloride, the maximal AFP level occurred on days three and four after administration. There was a significant correlation between the serum AFP level and the number of mitoses in the liver. (62 references)

3024 CARCINOEMBRYONIC ANTIGEN (CEA). IMMUNOCHEMICAL AND IMMUNOHISTOLOGICAL STUDY. (Fr.) von Kleist, S. (Cancer Res. Inst., Villejuif, France). *Bulletin du Cancer* 60(4):393-402, 1973.

Carcinoembryonic antigen (CEA) which is highly resistant to heat and acids, is a glycoprotein with a carbohydrate moiety constituting about 50% and a molecular weight ranging from 180,000 to 200,000. The sedimentation constant ranges between 6.8 and 8.2 S. CEA must be distinguished from CEA-like substances which have immunologically active sites like those of CEA. Immunologically active glycopeptides with complete antigenic determinants of CEA are rich in N-acetyl-D-glucosamine, aspartic acid, and glutamic acid or glutamine. The asparagine-N-acetylglucosamine bond is the immunodominant site of CEA. The quantity of CEA decreases in the gastrointestinal tissues as one moves in a cephalad direction along the gastrointestinal tract. The antigen occurs most commonly in well-differentiated epitheliomas, while poorly differentiated or anaplastic tumors are often negative in immunofluorescence tests for CEA. The specificity of CEA is based on significant quantitative differences in its concentration in tumors and in normal colon. In addition to normal colon, CEA has been detected in various tumors and tissues outside of the gastrointestinal tract. CEA is not an autoantigen and does not stimulate immune reactions *via* cellular mediation. No blast transformation occurs in lymphocytes from patients with gastrointestinal cancers in the presence of pure CEA. (18 references)

3025 SOME NEWER ENDOCRINE ASPECTS OF BREAST CANCER. (E.) Jensen, E. V. (U. Chicago, Ill.). *N Engl J Med* 291(23):1252-1253, 1974. (No references)

3026 THE ADVANTAGES OF DROSOPHILA FOR MUTATION STUDIES. (E.) Sobels, F. H. (Dept. Radiat. Genet., Chem. Mutagen., U. Leiden, Netherlands). *Mutat Res* 26(4):277-284, 1974. (40 references)

3027 DEVELOPMENTS IN MONITORING HUMAN POPULATIONS FOR MUTATION RATES. (E.) Neel, J. V. (U. Michigan Med. Sch., Ann Arbor). *Mutat Res* 26(4):319-328, 1974. (16 references)

3028 MODULATORY EFFECT OF CYTOSTATICS AND CHEMICAL CARCINOGENS ON LIVER REGENERATION. (A REVIEW). (E.) Cihak, A. (Czechoslovak Acad. Sci., Prague) and H. M. Rabes. *Neoplasma* 21(5):497-518, 1974. (175 references)

3029 REMARKS ON THE MORPHOLOGY OF GONADOBLASTOMA. (E.) Motlik, K. (Fac. Gen. Med., Charles' U., Prague, Czechoslovakia), J. Marek and L. Starka. *Patol Pol* 25(2):237-241, 1974. (No references)

3030 CONGENITAL AND INFANTILE NEOPLASIA OF THE KIDNEY. (E.) Bolande, R. P. (Dept. Pathol., McGill U., Montreal, Canada). *Lancet* 2(7895):1497-1499, 1974. (34 references)

3031 QUESTIONS OF HALOETHER CARCINOGENICITY. (E.) Drake, J. J. P. (British Biol. Res. Assoc., Surrey, England). *Food Cosmet Toxicol* 12(4):551-552, 1974. (No references)

- 3032 MAMMARY TUMORIGENESIS IN CHEMICAL CARCINOGEN-TREATED MICE. I. INCIDENCE IN BALB/C AND C57BL MICE. (E.) Medina, D. (Baylor Coll. Med., Houston, Tex.). *J Natl Cancer Inst* 53(1):213-221, 1974.

Inbred BALB/cCrg1 and C57BL/Ki mice were subjected to a pituitary isograft procedure, and 4 wk later were treated with urethan (20 mg in the drinking water or i.p.), 3-methylcholanthrene (MCA), or 7,12-dimethylbenz(a)anthracene (DMBA) (0.5 or 1.0 mg, intragastrically once weekly for 3-6 wks). Among BALB/c mice treated with 6 mg DMBA, mammary hyperplastic alveolar nodules (HAN) were rare, occurring in only 30% of the animals (an average of only one/mouse); mammary adenocarcinomas and adenoacanthomas were observed in 68% of these animals. The mammary tumor incidence was 32% and HAN were rare in C57BL mice treated with 6 mg DMBA. Neither mammary tumors nor HAN were seen in BALB/c mice treated with MCA, and only 5% of the MCA treated C57BL mice developed mammary tumors. HAN were found in 50% of the C57BL mice treated with urethan, but only one of 11 animals treated for 20 months with urethan developed a mammary tumor. Atypical intraductal hyperplasias were seen in both strains, particularly C57BL mice exposed to urethan. A third type of mammary dysplasia seen in carcinogen-treated BALB/c mice was characterized by squamous metaplasia of the mammary alveoli. These lesions showed mononuclear cell infiltration, varying degrees of fibrosis, and significant areas of pyknotic nuclei.

- 3033 MAMMARY TUMORIGENESIS IN CHEMICAL CARCINOGEN-TREATED MICE. II. DEPENDENCE ON HORMONE STIMULATION FOR TUMORIGENESIS. (E.) Medina, D. (Baylor Coll. Med., Houston, Tex.). *J Natl Cancer Inst* 53(1):223-226, 1974.

At age 4 wk inbred BALB/cKi received a single pituitary isograft under the kidney capsule, and 4 wk later were started on a 2 or 5 wk program of 3-methylcholanthrene (MCA) treatment (0.5 or 1.0 mg weekly, intragastrically). The pituitary isograft was removed at age 10 wk, immediately after the last carcinogen treatment, or at age 16 wk. Some mice with the graft removed at 10 wk received a 2nd graft at 16 wk, and this was removed at 28 wk. A final group were given a pituitary isograft only after (6 wk) carcinogen treatment. None of the mice developed hyperplastic alveolar nodules or ductal hyperplasia. Hormone stimulation was important for the induction of mammary tumors by MCA. Tumor incidence at the lower dose was 0% in mice given a pituitary isograft only after carcinogen treatment, 50% in mice with the isograft removed after the last treatment, and 82% both in mice retaining the graft for 16 wk and mice receiving a 2nd graft at 16 wk. The response to MCA was dose-dependent: 6 mg produced 91% tumors at 6.5 months, while 1.5 mg produced 82% tumors but at 13 months. The mammary tumors which arose during prolonged hormone stimulation or immediately thereafter were adenoacanthomas, whereas tumors which arose later were predominately type-B adenocarcinomas.

- 3034 PHAGE AND BACTERIAL INACTIVATION AND PROPHAGE INDUCTION BY CHEMICAL CARCINOGENS. (E.) Yamamoto, N. (Temple U. Sch. Med., Philadelphia, Pa.), M. D. Anderson and J. A. DiPaolo. *Mol Pharmacol* 10(4):640-647, 1974.

The ability of various water-soluble and insoluble carcinogens to cause prophage induction and decrease colony formation in several strains of *Salmonella typhimurium* was studied. The maximum prophage induction frequency for each carcinogen was determined by the ratio of the number of induced phage particles relative to that of spontaneously induced phage particles in control cultures. This value was constant for each carcinogen, regardless of its concentration. Since damage of the bacterial genome results in prophage induction, the reactivity of each compound with the genome was indicated by the minimum concentration required for prophage induction and the maximum frequency of prophage induction. Carcinogens which were unable to affect bacterial viability were also unable to induce prophage, with failure to induce prophage indicating a requirement for metabolic activation by mammalian enzymes. Interaction of 16 carcinogens with free phage particles *in vitro* was used as an index of the direct interaction of carcinogen with DNA. Of the compounds tested, six had a direct effect on the phage genome, resulting in a loss of phage viability. Five of the six compound were hydroxylated compounds (4-hydroxyaminoquinoline 1-oxide, *N*-hydroxy-2-aminofluorene, α -hydroxyaminonaphthalene, β -hydroxyaminonaphthalene, and *N*-hydroxyurethane), and the other was *N*-acetoxy-2-acetylaminofluorene. Thus, these six compounds appear to be reactive with genomes without further metabolism.

- 3035 THE CARCINOGENIC AND COCARCINOGENIC EFFECT OF EXTRACTS FROM DRIED FRUIT. (Rus.) Ruchkovskii, B. S. (Inst. Problems Oncol., Kiev, USSR), L. A. Tiktin and T. N. Oleinikova. *Vopr Onkol* 20(4):58-61, 1974.

The carcinogenicity and cocarcinogenicity of benzene extracts from prunes were tested in noninbred male mice. Prunes, which had been dried either in a tunnel apparatus or in an oven, were extracted in a Soxhlet apparatus with benzene. Extracts from oven-dried prunes contained 1 g/ml benzo(a)pyrene (BP), while those dried in a tunnel apparatus contained only 0.045 g/ml BP. Over a period of many years, no skin tumors had ever been observed in mice from this laboratory, and the incidence of other neoplasms was very low. When applied to the skin of 38 mice two to three times/wk for nine months, extracts from these prunes produced a papilloma in only one mouse; this papilloma did not continue to grow or to undergo malignant transformation. When applied to the skin of mice together with a benzene solution of BP, extracts from prunes had a cocarcinogenic effect. While 6 of 15 (40%) mice treated with BP alone developed tumors, tumors developed in 12 of 14 (85.8%) mice treated with extract from oven-dried prunes. Of these tumors, two in the control group and three in each of

the experimental groups became malignant. It is concluded that the use of food products with even a minimal carcinogen content is particularly undesirable for people suffering from chronic inflammatory diseases of the gastrointestinal tract and other pre-cancerous gastrointestinal diseases.

3036 THE ENHANCEMENT OF BIPHENYL-2-HYDROXYLATION BY CARCINOGENS *IN VITRO*. (E.)

McPherson, F. J. (Dept. Biochem., U. Surrey, Guildford, England), J. W. Bridges and D. V. Parke. *Biochem Soc Trans* 2(4):618-619, 1974.

Studies were conducted on the effects of the addition *in vitro* of carcinogens and noncarcinogens on Syrian hamster or Wistar rat hepatic microsomal biphenyl hydroxylation. A number of carcinogens, including butter yellow, dimethylnitrosamine, aflatoxin B₁, 3-methylcholanthrene, 2-acetamidofluorene, and safrole significantly stimulated biphenyl 2-hydroxylation but had no effect or slightly inhibited biphenyl 4-hydroxylation. Compounds such as phenobarbitone, nikethamide, aniline, and 1,2,3,4-dibenzopyrene, which are probably not carcinogenic to hamsters and rats, had no effect on biphenyl 2-hydroxylation. These results imply that enhanced biphenyl 4-hydroxylation requires microsomal enzyme synthesis *de novo* whereas enhanced biphenyl 2-hydroxylation does not.

3037 BIOASSAYS OF CARCINOGENICITY AFTER FRACTIONATION OF CIGARETTE SMOKE CONDENSATE.

(E.) Lazar, P. (Stat. Res. Unit, I.N.S.E.R.M., Villejuif, France), I. Chouroulinkov, C. Izard, P. Moree-Testa and D. Hemon. *Biomedicine* 20(3):214-222, 1974.

The counter-current fraction of cigarette smoke condensate (CSC) produces six fractions, the carcinogenicity of which were determined using bioassay procedures in IC mice. In one procedure, the various fractions were applied alone or in different combinations to the shaved skin of the mice and the development of cutaneous tumors was monitored. In the second procedure, sebaceous gland suppression and hyperplasia of the epidermis was monitored after only 3 or 4 applications. CSC fractions I and II were both active in the short-term hyperplasia test; they contained only promoting substances but probably included the major proportion of these. Fraction III contained an important proportion of the initiating substances present in CSC and some of the residual promoting compounds; it was somewhat less active than fraction II in the sebaceous gland test. Fraction IV was practically inactive in both tests. The subfractionation of fraction II permitted the isolation of subfraction II-2, which was more active than two other subfractions in the short-term tests, and the subfractionation of fraction III confirmed the activity of the polycyclic aromatic hydrocarbons (PAH) in the sebaceous gland test.

3038 PENETRATION OF THE RESPIRATORY EPITHELIUM OF GUINEA PIGS FOLLOWING EXPOSURE TO CIGARETTE SMOKE. (E.) Simani, A. S. (Dept. Path., McGill U., Montreal, Canada), S. Inoue and J. C. Hogg. *Lab Invest* 31(1):75-81, 1974.

The ability of the guinea pig respiratory epithelium to exclude the electron microscopic tracer, horseradish peroxidase, was observed following exposure to various levels of cigarette smoke (0 to 600 cigarettes; maximum exposure, 10 cigarettes per day). Horseradish peroxidase did not normally penetrate the respiratory epithelium, but, following exposure to cigarette smoke, penetration was observed at all levels. This penetration occurred at low levels of exposure (50 cigarettes) in the bronchioli and alveoli and at higher levels of exposure (270 cigarettes) in the trachea. Maximum penetration occurred after exposure to 200 cigarettes in the bronchioli and alveoli and after 400 cigarettes in the trachea. The mechanism of transport of the tracer into the epithelial intercellular spaces is not completely clear, but the most likely explanation appears to be a loosening or opening of the epithelial tight junctions. These data indicate that cigarette smoke interferes with the normal protective function of the respiratory epithelium and that this change occurs before there is any metaplastic or neoplastic change in the epithelium. Thus, the important early change in the epithelium may be a loss of protective function which could allow the carcinogens present in cigarette smoke to penetrate to the basal layer of cells and the basement membrane.

3039 THE pH OF TOBACCO SMOKE. (E.)

Brunnemann, K. D. (American Hlth. Fdn., New York, N.Y.) and D. Hoffmann. *Food Cosmet Toxicol* 12(1):115-124, 1974.

The pH of various tobacco products and the factors in tobacco most likely to determine pH of the smoke are reported. The pH was determined by puffing smoke over a highly sensitive combination electrode. The total mainstream smoke of some domestic, foreign, and experimental cigarettes, as well as of some cigars and little cigars was measured. Total nitrogen, total alkaloids, and total volatile bases of the tobacco showed a high degree of correlation with the pH of the mainstream smoke. The findings are discussed with regard to tobacco-smoke toxicity and inhalability.

3040 DISTURBANCES IN TRYPTOPHAN METABOLISM AFTER A SINGLE DOSE OF AFLATOXIN B₁ AND CHRONIC INTOXICATION WITH CARBON TETRACHLORIDE.

(E.) Lemonnier, F. J. (Groupe U56, INSERM, Hopital Bicetre, France), J. M. Scotto and C. Thuong-Trieu. *J Natl Cancer Inst* 53(3):745-749, 1974.

Female Wistar rats were given a single dose (half the LD₅₀) of aflatoxin B₁, by gastric gavage, either alone or in combination with chronic intox-

ication with carbon tetrachloride (CCl_4 , daily inhalation for 8 months). Histologic and biochemical studies were conducted during the subsequent 30 months. An L-tryptophan load (10 mg/100 g rat, by gavage) was administered and the urinary excretion of certain of its metabolites was evaluated. The activity of hepatic tryptophan-oxygenase and the quantity of nucleic acids were determined when the animals were killed. The percentage of animals with abnormal test results was significantly higher in the groups given aflatoxin or CCl_4 + aflatoxin than in a control group. Furthermore, the association of the two toxic substances increased all biochemical parameters and induced earlier and more intense histologic modifications. The number of hepatomas, however, was virtually identical in all groups. The biochemical anomalies observed probably resulted more from the administration of the toxic substance(s) than from the neoplastic process.

3041 AFLATOXIN Q_1 : A MAJOR METABOLITE OF AFLATOXIN B_1 PRODUCED BY HUMAN LIVER. (E.)

Buchi, G. H. (Dept. Chem., Massachusetts Inst. Technol., Cambridge), P. M. Muller, B. D. Roebuck and G. N. Wogan. *Res Commun Chem Pathol Pharmacol* 8(4): 585-592, 1974.

Aflatoxin Q_1 , a compound whose structure had not previously been established, represents a quantitatively important metabolic derivative of aflatoxin B_1 produced *in vitro* by human and monkey liver. The 900xg supernatant of a fresh human liver sample converted B_1 to Q_1 with an efficiency of about 30% in 30 min. Preparative-scale incubations of human and monkey liver preparations resulted in the isolation of a sufficient quantity (23 mg) of Q_1 for structure elucidation. It was established that Q_1 is a monohydroxylated derivative of B_1 , with the hydroxyl group on the carbon atom in the position β to the carbonyl of the cyclopentenone ring.

3042 CANCER SCARE SPREADS TO ARSENIC PRODUCTS IN U.S. (E.) Wright, A. (No affiliation). *Chem Age* 108(2877):6, 1974.

Dow Chemical Co. and Allied Chemical Co. have furnished statistics which show a high rate of cancer deaths among workers exposed to arsenic. A study of deaths of 22 retired workers from an Allied Chemical arsenic compounds plant showed that 17 were caused by cancer, including 10 from lung cancer and three from lymphoma. The expected number of deaths among the 22 workers was only 1.2. The death rate from lung cancer was 7 times and that from lymphoma was 6 times the expected. All workers had been exposed to compounds containing arsenic trioxide for from 10 to 30 yr. Recently, it was suggested by the National Institute for Occupational Safety and Health that the legal maximum for arsenic exposure in U.S. plants be lowered from 0.5 mg/m³ air to 0.05 mg/m³. To reduce the risk, the Allied plant has changed

operations to substitute production of liquid arsenicals for solid forms.

3043 EVALUATION OF POLLUTION CAUSED BY ASBESTOS: ASBESTOS FROM AUTOMOBILES. (Fr.)

Dingeon, M. J. (Courmont Hosp., Pierre-Benite, France) and Collombel. *Pollut Atmos* 16(62):183-190, 1974.

Sources of and health damages caused by asbestos in the environment are reviewed with special regard to asbestos released by vehicles with asbestos-containing brake linings. Asbestos, inhaled or digested, was found to cause bronchopulmonary cancer, pleural and peritoneal mesothelioma, and cancer of the stomach and colon, especially in subjects occupationally exposed to asbestos. Crocidolite and anthophyllite were found to be more powerful carcinogens than chrysotile which in its synthetic form is practically harmless. Tobacco, irritation of the respiratory tract, manganese, beryllium, magnesium, iron, nickel, chromium, and cobalt, as well as possibly tar, mineral oils, and benzopyrene are regarded as cofactors in asbestos-induced carcinogenesis. Asbestos was found in river water in concentrations up to 23.4 $\mu\text{g/gallon}$ in the USA, and asbestos concentrations ranging from 0.1-100 ng/cu m were measured in city air. The asbestos released by drum brakes was found to have lost its optical and carcinogenic properties. In addition, much of the asbestos worn off from drum brakes accumulates inside the brake, while asbestos released by disk brakes is emitted to the atmosphere nearly quantitatively.

3044 SEMIQUANTITATIVE STUDY OF ASBESTOS DUST CONCENTRATION IN 14 CASES OF PLEURAL

MESOTHELIOMA. (Fr.) Fondimare, A. (Reg. Hosp. Ctr., Le Havre, France), J. Desbordes, J. Perrotey, J. Tayot, and J.-L. Ernoult. *Arch Anat Pathol (Paris)* 22(1):55-60, 1974.

Fourteen cases of pleural mesothelioma were analyzed by microscopic, electron microscopic, and electron diffraction techniques to establish relationships between exposure to asbestos dust and the presence of ferruginous bodies. The mesotheliomas were unilateral, diffuse, and of pseudosarcomatous, epithelial, or mixed types. Light microscopic examinations of dissolved tissue samples on millipore filters revealed ferruginous bodies in 12 cases. The ferruginous body count was below 100/4 g sample in 3 cases, between 100 and 1,000 in another 3 cases, and over 1,000 in 6 cases. The latter 9 patients had been occupationally exposed to asbestos, and all 14 patients had been exposed to asbestos dust concentrations well above the background level. The exposure to asbestos had ceased 20-40 yr before the first clinical manifestations of the pleural alterations. Chrysotile and amosite were tentatively identified in the ferruginous bodies by electron diffraction analysis.

3045 THE OXIDATION OF SOME CARCINOGENIC ARYLHYDROXYLAMINES TO NITROSO DERIVATIVES WITH MANGANESE DIOXIDE. (E.) Brill, E. (U. Miami, Sch. Med., Fla.). *Experientia* 30(7):835, 1974.

Activated manganese dioxide converts N-phenylhydroxylamine to nitrosobenzene and 6-hydroxylaminopurine to 6-nitrosopurine in very high yields in 10-15 min when chloroform is used as a reaction-medium in concentration sufficient to effect complete solution of the arylhydroxylamines. The yield and purity of the nitroso compound is dependent on the purity of the arylhydroxylamine. The experimental procedure involves adding 2 equivalents of activated manganese dioxide to freshly prepared arylhydroxylamine in chloroform. The suspension is stirred vigorously under nitrogen for 15 min. The following nitroso compounds were prepared: 1-nitrosonaphthalene, 2-nitrosonaphthalene, 4-nitrosobiphenyl, 2-nitrosofluorene, nitrosobenzene, and 3-nitrosodibenzofuran.

3046 INHIBITION BY N-HYDROXY-2-ACETYLAMINOFLUORENE OF INCORPORATION OF [5-³H]OROTIC ACID INTO RNA OF TWO CLASSES OF NUCLEI FROM NORMAL AND REGENERATING LIVER. (E.) Glazer, R. I. (Dept. Pharm., Emory U., Atlanta, Ga.). *Biochim Biophys Acta* 361 (3):361-366, 1974.

The incorporation of [5-³H]orotic acid into ribosomal (rRNA) and heterogeneous nuclear (HnRNA) RNA of normal and regenerating parenchymal and nonparenchymal liver cells was studied in male Sprague-Dawley rats given N-hydroxy-2-acetylaminofluorene (2-AAF, 20 mg/kg i.p. for 2 hr). Maximal rate of incorporation of precursor into HnRNA of parenchymal and nonparenchymal nuclei of regenerating liver occurred at 6 and 20 hr, resp. Maximal rate of incorporation into rRNA of both classes of nuclei was seen after 6 hr; however, the relative increase of label incorporated into rRNA of nonparenchymal nuclei between 2-20 hr after partial hepatectomy was greater than that into parenchymal nuclear rRNA. The percentage distribution of total radioactivity incorporated into each RNA fraction did not differ as a result of liver regeneration; rRNA concentration, however, increased by about 40% in parenchymal cells. Treatment of normal mice with 2-AAF inhibited incorporation of label into rRNA and HnRNA to about the same extent in parenchymal (40-49%) and nonparenchymal (57-59%) nuclei. However, compared to the inhibition by AAF of incorporation into normal liver, AAF produced a 3-fold greater inhibition of incorporation into rRNA of parenchymal nuclei of regenerating liver. Incorporation of label into rRNA of regenerating nonparenchymal nuclei and into HnRNA of both types of regenerating nuclei showed about the same degree of inhibition by 2-AAF as that produced in normal liver. These results indicate that nonparenchymal nuclei have a greater proliferative capacity than do parenchymal nuclei and that 2-AAF cytotoxicity is not restricted to one liver cell type.

3047 EARLY ELEVATION OF α_1 -FETOPROTEIN IN N-2-FLUORENYLACETAMIDE HEPATOCARCINOGENESIS. (E.) Becker, F. F. (New York U. Sch. Med., N.Y.) and S. Sell. *Cancer Res* 34(10):2489-2494, 1974.

Serum α_1 -fetoprotein levels were studied by radioimmunoassay in SD and F/344 rats fed a diet containing N-2-fluorenylacacetamide (FAA). SD rats which received a single 3-wk exposure to 0.06% FAA, a dose corresponding to about 25% of the carcinogenic concentrations, showed significantly elevated α_1 -fetoprotein levels after one wk in females and after two wk in males, continuing to rise to 644 ng/ml and 1100 ng/ml, resp., after cessation of FAA feeding. Maximal levels were reached after 28 days, remained at this level until about the 10th wk, and returned to normal (24-39 ng/ml) by the 29th wk. In other experiments, rats were fed either 0.045, 0.03, or 0.015% FAA for 42 days or 0.06% for two feeding cycles of three wk, each interposed by one wk of normal diet. In all cases, animals responded with elevated α_1 -fetoprotein in a manner similar to the first experiment. Histologic sections of liver from experimental rats following cessation of the FAA diet revealed basophilic foci in males but none in females. Mortality rate reflected the histologic findings. Exposure of male SD rats to various low FAA concentrations for 60 days showed a dose-dependent effect on both the time of initially detectable increased α_1 -fetoprotein and the rate of increase, with maximal levels being 175, 115, and 98 ng/ml for 0.005, 0.001, and 0.0005% FAA, resp. Rats receiving 0.0001% FAA showed no rise in α_1 -fetoprotein. Acute administration of 0.03 or 0.015% FAA for three wk to female F/344 rats which have deficient liver hydroxylating capacity resulted in a delayed stimulation of serum α_1 -fetoprotein production suggesting that hydroxylation of FAA is required for its stimulatory effect.

3048 IMPORTANCE OF TESTES IN INDUCTION OF HYPERPLASTIC NODULES, CARCINOMAS, AND CIRRHOSIS OF LIVER IN A x C MALE RATS INGESTING 0.025% N-2-FLUORENYLDIACETAMIDE. (E.) Reuber, M. D. (Natl. Cancer Inst., Bethesda, Md.). *J Natl Cancer Inst* 53(3):883-886, 1974.

The dependence of hepatic carcinogenesis on the testes was studied in inbred A x C male rats ingesting 0.025% N-2-fluorenyldiacetamide (F-diAA) for 4 wk. The experimental groups consisted of intact rats with normal testes, rats with one normal testis, rats with one atrophic testis related to a congenital defect, and rats without testes. The incidence of carcinomas and the number of rats with large carcinomas, multiple carcinomas, and metastases were highest in the intact rats. The incidence and size decreased in animals with one or both testes removed, and the decrease was directly related to the bulk and weight of the testis in the rats in the other groups. The incidence was lowest in the rats with both testes removed. This experiment confirmed the importance of the testes in F-diAA hepatic carcinogenesis, and also demonstrated the extreme sensitivity of the liver to the level of male sex hormone.

- 3049 EFFECT OF *N*-2-ACETYLAMINOFLUORENE MODIFICATION ON THE CONFORMATION OF NUCLEIC ACIDS. (E.) Levine, A. F. (Columbia U. Coll. Phys. Surg., New York, N.Y.), L. M. Fink, I. B. Weinstein and D. Grunberger. *Cancer Res* 34(2):319-327, 1974.

Previous studies on the structural and functional properties of oligonucleotides and transfer RNA modified *in vitro* by *N*-acetoxy-*N*-2-acetylaminofluorene (AAAF) led to a proposal of a specific conformation for the structure of nucleic acids in the region to which the acetylaminofluorene residue is covalently bound. This structure had been designated "the base displacement model." The present study extends this analysis to the effects of drug modification on DNA, reovirus RNA, ribosomal RNA, and polyadenylic acid. The rate and extent of reaction of denatured DNA with *N*-2-acetylaminofluorene (AAF) were 2 to 3 times greater than with native DNA; a high ionic environment (0.1 M NaCl), which is known to stabilize nucleic acid secondary structure, decreased the rate and extent of nucleic acid modification. AAF-modified native DNA exhibited a decrease in thermal stability and intrinsic viscosity and a tendency to elute at lower salt concentration from a hydroxyapatite column. The susceptibility of double-stranded reovirus RNA to ribonuclease digestion was increased by modification with AAF, and modified *Escherichia coli* ribosomal RNA was impaired in its ability to hybridize to homologous DNA. These findings indicate that modification of high-molecular-wt double-stranded nucleic acids produces localized regions of denaturation, a finding consistent with the base displacement model. In addition to covalent binding of AAAF to nucleic acids, extensive noncovalent binding to native DNA and polyadenylic acid was observed.

- 3050 SELECTIVE INDUCTION OF MIXED FUNCTION OXIDASES IN HEPATIC MICROSOMES. I. COMPARISON BETWEEN ACETYLAMINO-2-FLUORENE AND ACETYLAMINO-4-FLUORENE. (Fr.) Roberfroid, M. (Pharm. Sch., Univ. Louvain, Belgium), J. C. Tancredi, G. Dubmoi and M. Mercier. *Arch Int Physiol Biochim* 82(1):197-198, 1974.

The biochemical action of acetyl amino-2-fluorene and acetyl amino-4-fluorene on mixed function oxidases in rat hepatic microsomes was studied *in vitro*, using phenobarbital and methyl-3-cholanthrene as reference inducers. The glucose-6-phosphatase, cytochrome oxidase, NADH- and NADPH cytochrome *c* reductase activities and distributions were measured in the E, N, ML, P, and S subcellular fractions of rat liver homogenates, and a kinetic study was carried out of the aminopyrine demethylase, aniline hydroxylase, and aldrin epoxidase activities in the microsomal P fraction. The cytochrome P-450 and b5 levels were measured in the same fraction. The preliminary results indicate differences in the action of the two isomers regarding both the distribution of the enzymes and the activities of the mixed function oxygenases. Acetyl amino-2-fluorene was found to have selective inductive effect on the flavoprotein component (NADPH-cytochrome *c* reductase).

- 3051 METHYLMERCAPTO-4-ACETYLAMINOSTILBENES AS PRODUCTS OF THE REACTION OF *N*-ACETOXY-4-ACETYLAMINOSTILBENE WITH METHIONINE AND AS DEGRADATION PRODUCTS OF LIVER PROTEIN FROM RATS GIVEN *N*-HYDROXY-4-ACETYLAMINOSTILBENE. (E.) Miller, E. C. (U. Wisconsin Med. Ctr., Madison), B. W. Butler, T. L. Fletcher and J. A. Miller. *Cancer Res* 34(9):2232-2239, 1974.

The reaction of the carcinogenic electrophile *N*-acetoxy-4-acetylaminostilbene with methionine at neutral pH yielded β -methylmercapto-4-acetylaminostilbene as the major product and 3-methylmercapto-4-acetylaminostilbene as a minor product. Two other products were also formed. One of these had the apparent molecular weight (283) of a methylmercapto-4-acetylaminostilbene; it was not identical with 2-, 2', 3', or 4'-methylmercapto-4-acetylaminostilbene. The second product had an apparent molecular weight of 301 and appeared to be a methylmercapto derivative. It was formed in larger amounts at slightly acid pH's, and its yield was inversely related to that of β -methylmercapto-4-acetylaminostilbene. 3- and β -methylmercapto-4-acetylaminostilbene were also obtained on alkaline degradation of the liver protein from rats that had received i.p. injections of *N*-hydroxy-4-acetylaminostilbene. These data provide evidence that an ester of *N*-hydroxy-4-acetylaminostilbene or a derivative with similar electrophilic reactivity is formed from *N*-hydroxy-4-acetylaminostilbene in the rat liver.

- 3052 TWO-DIMENSIONAL GEL ELECTROPHORESIS OF ACID-EXTRACTABLE NUCLEAR PROTEINS OF REGENERATING AND THIOACETAMIDE-TREATED RAT LIVER, MORRIS 9618A HEPATOMA, AND WALKER 256 CARCINOSARCOMA. (E.) Yeoman, L. C. (Baylor Coll. Med., Houston, Tex.), C. W. Taylor and H. Busch. *Cancer Res* 34(2):424-428, 1974.

Two-dimensional polyacrylamide gel electrophoresis was used to analyze acid-soluble nuclear proteins extracted with 0.4N H₂SO₄ from citric acid-isolated nuclei of Morris 9618A hepatoma, Walker 256 carcinosarcoma, and from regenerating liver and liver from Holtzman rats treated daily for 9 days with thioacetamide (50 mg i.p.). Although most of the protein spots were common to the livers and tumors studied, all of the rodent tumors were similar in their marked density of Spots C16-C18 found in the area of nuclear proteins migrating the slowest in both directions. In normal, regenerating, and thioacetamide-treated liver, the spots in this region were much less dense.

- 3053 THE DEVELOPMENT OF LEUKEMIA AFTER EXPOSURE TO BENZENE AND PHENYLBUTAZONE. (Ger.) Hartwich, G. (Med. Clin. Polyclin., U. Erlangen, Germany) and H. Lutz. *Verhandl Dtsch Ges Inn Med* 79:394-396, 1973.

Attention is drawn to the role of benzene and drugs containing pyrazole radicals, such as phenylbutazone and aminopyrene, in the development of leukemia. Of

5 patients, three developed leukemia after exposure to benzene for periods of 24 to 39 yr. Each patient first developed pancytopenia which turned into acute leukemia. Two brothers developed pancytopenia and leukemia after taking 30 g phenylbutazone and 30 to 40 g aminopyrene over 4 to 6 yr for rheumatoid arthritis. The development of leukemia in these two brothers suggests that there is an individual predisposition to leukemia since, with the widespread use of phenylbutazone, leukemia and pancytopenia would otherwise be more common.

3054 CHRONIC MYELOID LEUKEMIA IN A 35-YEAR-OLD PETROLEUM CHEMIST WHO HAD BEEN EXPOSED TO BENZENE SINCE THE AGE OF 18. (Fr.) Liaudet, J. (Hosp. Ctr., Le Havre, France) and M. Combaz. *Eur J Toxicol* 6(6):309-313, 1973.

A 35-yr-old petroleum chemist, who had worked with small quantities of heptane, benzene, toluene, and ketones for 17 yr, developed chronic myeloid leukemia. A chromosome study showed the possible existence of a Philadelphia chromosome. Within less than three months, treatment with busulfan gave a clinical and hematological remission which has been maintained for 41 months by reinduction every six months by a combination of hydroxyurea-mercaptopurine and prednisone. Although it has not been conclusively demonstrated that benzene causes chronic myeloid leukemia, it seems likely in this case because of the duration of the patient's exposure.

3055 SPECTROPHOTOMETRIC ANALYSIS OF CYTOCHROMES IN RAT LIVER DURING CARCINOGENESIS. (E.) Oyanagui, Y. (Sch. Med., Osaka U., Japan), N. Sato and B. Hagihara. *Cancer Res* 34(3):458-462, 1974.

The cytochrome content of male Sprague-Dawley rat liver mitochondria and microsomes during carcinogenesis by both 3'-methyl-4-dimethylaminoazobenzene (3'-DAB) and 4'-methyl-4-dimethylaminoazobenzene (4'-DAB), and of 3'-DAB-induced hepatomas, was determined spectrophotometrically at room and liquid nitrogen temperatures and was compared with that of normal liver. Experimental groups were fed the carcinogenic M-diet containing 0.06% each of 3'-DAB and 4'-DAB. The cytochrome $a + a_3$ content in the livers of rats fed the standard amounts of 3'-DAB or 4'-DAB began to decrease from the 16th wk. At the 27th wk the cytochrome content approached the level of the 3'-DAB-induced hepatoma, which is nearly 1/2 that in normal liver. Conversely, the content of cytochromes b , c_1 , and c did not change significantly during liver carcinogenesis by 3'-DAB and 4'-DAB, or in the 3'-DAB-induced hepatoma. The ratio of cytochrome $a + a_3$ to cytochrome c of mitochondria in liver decreased from 1.1 to 0.6 in the precancerous state and finally reached 0.5 in the hepatoma. The microsomal cytochrome b_5 and P-450 content did not alter gradually during carcinogenesis but decreased abruptly in the hepatoma.

3056 THE EFFECT OF 4-DIMETHYLAMINOAZOBENZENE (DAB) ON THE MITOCHONDRIA OF THE CELLS CULTIVATED IN TISSUE CULTURE. II. THE EFFECT OF 4-DIMETHYLAMINOAZOBENZENE (DAB) ON MITOCHONDRIAL ENZYMES. (E.) Enginun, M. (Radiobiol. Dept., Cekmece Nuclear Res. Training Ctr., Turkey) and E. Ucer. *Istanbul Universities* 38(1/4):87-89, 1974.

48-Hr embryonic rat cells were incubated in medium containing calf serum and 1 mg/ml 4-dimethylaminoazobenzene (DAB); the cells were then washed and incubated in medium containing no DBA. The activities of isocitrate (ICDH) and glutamate (GLDH) in the mitochondria of the DAB-treated cells increased with increasing incubation time (1.5, 3, 5, and 24 hr) in medium containing DAB; this effect was more pronounced with ICDH than with GLDH. Upon removal of DAB from the incubation medium, the enzyme activities, particularly that of ICDH, decreased. The increases in enzyme activity observed during incubation with DAB are similar to those observed in tumor tissues, although the activities are higher in the tumor cells than in any of the DAB-treated cells. The data indicate that the effect of DAB is on the enzymes themselves and the mitochondrial metabolism rather than on the mitochondrial membrane.

3057 PROPERTIES OF THE PRINCIPAL LIVER TARGET PROTEIN OF A HEPATIC CARCINOGEN. (E.) Sani, B. P. (Fox Chase Ctr. Cancer Med. Sci., Philadelphia, Pa.), D. M. Mott, V. Jasty, and S. Sorof. *Cancer Res* 34(10):2476-2481, 1974.

The physical and biological properties of the principal liver target protein of a hepatic azocarcinogen, 3'-methyl-4-dimethylaminoazobenzene (3'-Me-DAB), were studied. The azoprotein was purified for analysis from liver cytosol fractions prepared from male CFN rats fed a diet for 15-18 days containing 0.058% 3'-Me-DAB and was identified by precipitation with specific absorbed antiserum. When liver cytosol protein from untreated controls was fractionated on Sephadex G-200 columns and tested for the presence of target protein by double radial immunodiffusion against specific antiserum, target protein was detected only in the 5S component, the molecular weight being estimated at 60,000-80,000. Electrophoretic analysis of target protein showed that it had the same properties as the principal azoprotein conjugate of liver cytosol of rats fed 3'-Me-DAB. Reduced and alkylated immunoprecipitates of the target protein from normal and 3'-Me-DAB-fed rats showed the same electrophoretic properties, indicating that both had the same subunit sizes. Experiments in which target protein turnover was estimated in control and 3'-Me-DAB-fed rats injected with guanido- ^{14}C -L-arginine indicated a half-life of 3.3 ± 0.1 days compared to a half-life of 2.5 ± 3.0 days previously reported for total liver proteins. Thus, the interaction of azocarcinogens with their principal target protein in rat liver does not appear to alter the target protein substantially.

- 3058 THE COMBINED ACTION OF BENZIDINE AND 2-NAPHTHYLAMINE. (Rus.) Pliss, G. B. (N. N. Petrov Sci. Res. Inst. Oncol., Leningrad, USSR) and M. G. Iogannsen. *Vopr Onkol* 20(8): 69-71, 1974.

Studies were made of the combined action of carcinogens in mature (120-140 g) white rats on a normal diet. In the first series, 20 females and 30 males were injected s.c. with 2-naphthylamine (5 mg each); in the second, 16 females and 14 males were injected with benzidine (20 mg); and in the third, 30 females and 30 males were given benzidine and 2-naphthylamine. Injections were once/wk for 60 wk. In the first series, the total dose of 2-naphthylamine was 1200 mg. Tumors were observed in 16 animals (38%), including 11 sarcomas at the site of injection, lymphosarcomas and reticulum cell sarcomas of the mesentery in 2 rats, retroperitoneal fibrosarcoma in 1, reticulosis in 1. The average latent period was 570.6 days. In the second series, the total injected dose was 260 mg. Tumors were found in 23 animals (95.8%), primary multiple tumors in 9 rats (39.1%), mostly of cymbal glands (18 rats - 78.3%) and sarcomas at the site of injection (6 tumors - 26%). In the third series, the maximum doses of benzidine and 2-naphthylamine were 260 and 1040 mg resp. Tumors were found in 37 of 41 rats (90.2%), primary multiple tumors in 24 rats (64.8%), hepatic tumors in 21 rats (56.7%), cymbal gland cancer in 21 rats (56.7%), colonic tumors in 16 (43.2%). Evidence indicates that combined action increased considerably the incidence of intestinal and hepatic tumors with greater tendency to malignant transformation.

- 3059 FOCAL NODULAR HYPERPLASIA OF THE LIVER: POSSIBLE RELATIONSHIP TO ORAL CONTRACEPTIVES. (E.) Mays, E. T. (U. Louisville Sch. Med., Ky.), W. M. Christopherson and G. H. Barrows. *Am J Clin Pathol* 61(6):735-746, 1974.

Three resected solitary hepatic masses in noncirrhotic livers were studied histologically; all were taken from three 25 to 42-yr-old women who had been taking oral contraceptives (norethynodrel and mestranol) for several yr. The three lesions were histologically similar, the only variations noted being quantitative. These solitary masses appeared to represent focal nodular hyperplasia, and not benign hepatomas or hepatic adenomas, to which they bear a similarity. Various vascular lesions involving the afferent vessels, especially the interlobular branches of the portal vein, were noted; these changes may have had an etiologic role in the development of the masses. The vascular lesions could, in turn, be related to oral contraceptives. A fairly definite syndrome consisting of oral contraceptive ingestion, intrahepatic and/or intraperitoneal hemorrhage, shock or syncope, acute abdomen, and focal nodular hyperplasia of the liver (or benign hepatoma) has predominated in these and other cases thus far reported.

- 3060 BIOLOGICAL ACETYLATION OF A BENZIDINE IN SPRAGUE-DAWLEY RATS. (Fr.) Laham, S. (Ctr. Environ Hyg., Direction Gen. Hlth. Protection, Ottawa, Canada), E. Dulos, and W. Chang. *Biomedicine* 21(7):299-302, 1974.

The urinary excretion and metabolism of 3-methoxybenzidine in male Sprague-Dawley rats was studied by paper- and thin-layer chromatographic analysis. Following i.p. injection of a single 100 mg/kg dose in 1 ml corn oil, intact 3-methoxybenzidine appeared in the urine within the first 30 min, reached peak levels in the third hr, then declined considerably over the next two hr. A derivative acetylated in position 4' was present only during the second half-hr, and its level started dropping in the second hr. Sulfate ester of 3-hydroxybenzidine, eliminated at high rate during the first 3 hr, was determined to be the chief metabolite of 3-methoxybenzidine. The absence of the derivatives acetylated in position 4 indicates the strong steric inhibition of the acetylation of the NH_2 group. Intact 3-methoxybenzidine, the derivative monoacetylated in position 4', a diacetylated derivative, and sulfate ester of 3-hydroxybenzidine were identified in urine samples collected for 15 days following five daily injections of 100 mg/kg doses of 3-methoxybenzidine. The diacetylated derivatives were found only following repeated injections, which indicates that 3-methoxybenzidine stimulates its own metabolism in terms of biological acetylation. The formation of the diacetylated derivative is believed to be conditioned by the preceeding formation of the derivatives monoacetylated in position 4'. The high rate of elimination of the sulfate ester indicates the preponderant role of this route of metabolism in the biotransformation of carcinogenic amines.

- 3061 LIVER HAMARTOMAS IN PATIENTS ON ORAL CONTRACEPTIVES. (E.) O'Sullivan, J. P. (St. George's Hosp. Med. Sch. London, England) and R. P. Wilding. *Br Med J* 3(5922):7-10, 1974.

During the past 4 years, three cases of benign liver cell tumors in women who had been on oral contraceptives were seen at a London hospital. The first case involved a 34-yr-old woman who had taken lynestrenol-mestranol, ethyndiol-mestranol, and norethisterone-mestranol for 6 yr with two 12-month gaps, the second involved a 35-yr-old woman who had taken norethisterone-mestranol for 8 yr with two 18-month gaps, and the third involved a 51-yr-old woman who had taken an oral contraceptive for 8 yr. In each case there was a well circumscribed hypervascular mass of abnormally arranged liver tissue, the mass being composed of nodules of liver cell cords. There was marked proliferation of the bile ductular epithelium in the fibrous septa and in all three cases there were numerous dilated thin-walled blood vessels lined with endothelium. There was no evidence of bile retention or cirrhosis. All three specimens were reported as either hamartomatous nodules or hepatic malformations. Since October 1973, 11 other cases of

benign liver tumors in women who had taken oral contraceptives have been reported. The macroscopic appearances of the lesions were similar in all 14 cases. These tumors, although uncommon, are potentially fatal and the diagnosis must be considered in any patient who has clinical features of bleeding into the peritoneal cavity. Needle biopsy is contraindicated, liver scan and celiac arteriography being helpful in the diagnosis of the nonemergency case. Treatment in the emergency case is aimed at controlling blood loss with some form of liver resection. In the elective case, the choice is between local removal and a formal lobectomy, the former being preferred whenever possible.

3062 INFLUENCE OF DEAE-DEXTRAN, POLYBRENE, DEXTRAN AND DEXTRAN SULPHATE ON SPONTANEOUS LEUKAEMIA DEVELOPMENT IN AKR MICE AND VIRUS INDUCED LEUKAEMIA IN BALB/c MICE. (E.) Ebbesen, P. (Inst. Med. Microbiol., U. Copenhagen, Denmark). *Br J Cancer* 30(1):68-72, 1974.

Survival of AKR mice, which have a high incidence of spontaneous thymus lymphatic leukemia, was increased by weekly i.p. inoculations of 25 µg of the polycations diethylaminoethyl-dextran (DEAE-d), with or without poly I: poly C (0.5 U), or polybrene. Mean survival of mice treated with DEAE-d, polybrene, or DEAE-d + poly I:C was 10.2, 10.5, and 11.0 months, resp. Administration of the neutral dextran had no effect, whereas the polyanion dextran sulfate accelerated leukemia development. Lymphatic leukemia developed in 80-90% of the animals in all treatment groups; animals dying with leukemia had 25,000 leucocytes/µl while animals dying without leukemia had 7000 leucocytes/µl. Cell electrophoresis demonstrated that leukemic cells have a higher negative charge than normal cells and that *in vitro* cell contact with polycation or polyanion alters the overall cell charge in accordance with the charge of the polyion. The influence of weekly 25 µg inoculation of polycation/polyanion on survival time of adult BALB/c mice infected with Rauscher leukemia virus (10⁴ XC U) was also determined. DEAE-d, polybrene, and neutral dextran increased survival of mice treated from the time of palpable spleen enlargement 3 wk after infection. Treatment from the time of infection resulted in increased survival time of mice given dextran sulfate or neutral dextran.

3063 EFFECT OF PREPUBERAL ADRENALECTOMY ON THE MAMMARY TUMOR DEVELOPMENT AND HORMONAL STATUS OF TWO STRAINS OF MICE. (E.) Pai, S. R. (Cancer Res. Inst., Tata Memorial Ctr., Bombay, India). *Indian J Med Res* 62(6):845-850, 1974.

Prepuberal adrenalectomy was performed in two mammary cancer-susceptible strains of mice - C3H and ICRC. It failed to give any biological systemic effect in either strain but change was seen in the organ wt and in histology of C3H ovaries, pituitary

and thymus. The gonads of adrenalectomized C3H mice showed senile atrophy earlier than those of the intact C3H mice. The thymus and pituitary gland of adrenalectomized C3H mice were larger than those of intact littermate controls. Comparable changes appear to be absent in adrenalectomized ICRC mice. Mammary tumors developed in 62% of 16 adrenalectomized C3H mice but in none of 23 adrenalectomized ICRC mice. These observations further confirm the autonomous and hormone-independent nature of mammary tumor of C3H mice and suggest the hormone-dependent nature of mammary tumors of ICRC mice.

3064 EFFECT OF NEONATALLY ADMINISTERED ESTROGEN OR PROLACTIN ON NORMAL AND NEOPLASTIC MAMMARY GROWTH AND SERUM ESTRADIOL-17β LEVEL IN RATS. (E.) Nagasawa, H. (Natl. Cancer Cent. Res. Inst., Tokyo, Japan), R. Yanai, M. Shodono, T. Nakamura and Y. Tanabe. *Cancer Res* 34(10):2643-2646, 1974.

The effects of neonatal administration of estrogen or prolactin on 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumor growth and on serum estradiol-17β levels were studied in female Sprague-Dawley rats. Rats were given daily s.c. injections of estradiol 17β (10, 20, and 40 µg successively for 5 days each). At 60 days of age, the experimental groups received a single i.v. injection of 5 mg DMBA. At this time there was no difference in the degree of mammary growth between the experimental and control animals. All animals were sacrificed 120 days after DMBA injection. At this time, the mammary glands of both estrogenized and prolactinized rats had completely regressed. Whereas 55% of control rats had mammary tumors by this time, no tumors were observed in DMBA-treated, estrogenized or prolactinized animals. Serum estradiol-17β levels in estrogenized rats were significantly higher (7-19 pg/ml) than controls in diestrus (0-12 pg/ml) but significantly lower than in proestrus (10-43 pg/ml). Prolactinized animals had significantly higher estradiol levels (10-28 pg/ml) than diestrus controls but did not differ significantly from proestrus controls. These results suggest that regression of normal mammary tissue and complete suppression of tumorigenesis in DMBA-treated rats by estrogens and prolactins is due to the inhibitory effect of continuously elevated blood estrogen levels.

3065 DIFFERENTIAL SUSCEPTIBILITY OF FOUR MOUSE STRAINS TO INDUCTION OF MULTIPLE LARGE-BOWEL NEOPLASMS BY 1,2-DIMETHYLHYDRAZINE. (E.) Evans, J. T. (Roswell Pk. Mem. Inst., Buffalo, N.Y.), T. S. Hauschka and A. Mittelman. *J Natl Cancer Inst* 52(3):999-1000, 1974.

Inbred ICR/Ha, randombred ICR/Ha, DBA/2 and C57BL/Ha mice were treated with weekly s.c. injections of 1,2-dimethylhydrazine (15mg/kg) buffered with ethylene diamine-tetraacetic acid. After 20-22 weekly injec-

tions, all of the inbred ICR/Ha mice and 67% of the randombred ICR/Ha mice developed colonic adenocarcinomas. None of the DBA/2 or C57BL/Ha mice developed tumors. The randombred Swiss mice developed large adenomas with carcinoma *in situ*, while the inbred Swiss mice developed frankly invasive adenocarcinomas. Thus, strain specificity of an organotropic chemical carcinogenesis model has been established.

- 3066 THE EFFECT OF DEXTRAMYCIN ON THE TOXIC ACTION OF 7,12-DIMETHYLBENZO(a)ANTHRACENE AND ITS DERIVATIVES. (Rus.) T. A. Bogush (Inst. Exp. Clin. Oncology, Moscow, USSR); G. A. Belitskii and A. Ia. Khesina. *Vopr. Onkol.* 20(10):66-71, 1974.

Studies were carried out on the effect of chloramphenicol (CMP) and dextramycin (DMC) on the toxic action and rate of metabolism of 7,12-dimethylbenzo(a)anthracene (DMBA) in fibroblastoid cell culture in mice. CMP and DMC reduced the toxic effect of DMBA by 59% and 49%, resp. The incubation of cells with DMBA and CMP or DMC in the concentration of 500 µg/ml did not result in the summation of their toxic actions. CMP and DMC also inhibited the effect of DMBA on the morphological structure of the cells, particularly in the concentration of 500 µg/ml. The rate of metabolism of DMBA did not change with or without DMC (60% and 75%, resp.). To study the effect of DMC and of CMP on the adrenocortical action of DMBA in mice, random-bred female 100-140 g rats were force-fed 15-30 mg per animal of DMBA, 7-oxyethyl-12-methylbenzo(a)anthracene, or 7-acetoxymethyl-12-methylbenzo(a)anthracene. No necroses of the adrenal glands were found in any of the experimental animals that were given CMP or DMC 1.5-2 or 24 hours before the administration of DMBA or its derivatives. It is suggested that the protective effect of DMC is due to impairment of DMBA binding to nucleic acids.

- 3067 EFFECT OF CHLORAMPHENICOL ON THE METABOLISM OF CARCINOGENIC HYDROCARBONS AND BINDING TO CELLULAR MACROMOLECULES. (E.) Shabad, L. M. (Inst. Exp. Clin. Oncol., Acad Med. Sci., Moscow, USSR), G. A. Belitsky, T. A. Bogush and M. A. Panov. *Arzneim Forsch* 24(8):1177-1180, 1974.

The effect of chloramphenicol on the metabolism of two carcinogenic polycyclic hydrocarbons, 7,12-dimethylbenzo(a)anthracene (DMBA) and benz(a)pyrene (BP), and their binding to cell macromolecules was investigated in mouse embryo fibroblast-like cell cultures. Neither chloramphenicol nor its isomer dextramycin affected the rate of hydrocarbon metabolism. At the concentration of 500 µg/ml, however, chloramphenicol inhibited the binding of ³H-DMBA to DNA, RNA, and proteins. At the concentration of 100 µg/ml, this compound decreased somewhat the rate of the carcinogen bound to nucleic acids but not to proteins.

- 3068 CHANGES IN SECRETORY CELLS DURING EARLY STAGES OF EXPERIMENTAL CARCINOGENESIS IN THE RAT SUBMANDIBULAR GLAND. (E.) Kim, S.-K. (VA Hosp., Ann Arbor, Mich.), H. H. Spencer, L. Weatherbee and C. E. Nasjletti. *Cancer Res* 34(9):2172-2183, 1974.

Previous studies have shown that the local injection of 7,12-dimethylbenzo(a)anthracene induces largely squamous cell carcinoma in the rat submandibular gland. Cytological changes that occur initially in the secretory cells of the Sprague-Dawley rat submandibular gland following the injection of 1 mg 7,12-dimethylbenzo(a)anthracene were studied. One of the most striking features noted early in injected glands is the appearance of duct-like structures which appear to form by metaplastic transformation of secretory cells, mostly acinar cells. These structures are first noted about 2 wk after the injection, well before the first signs of cancer appear at about 14 wk and increase continuously in number. Radioautographic studies of injected glands indicated that a large number of acinar cells and cells of the duct-like structures become labeled with tritiated thymidine, suggesting an increased mitotic activity in these cells. The fine structural alterations seen in cells of the duct-like structures and in acinar cells undergoing metaplastic transformation are characteristic of those frequently associated with depressed protein synthesis. The secretory cells of the control gland do not reveal the alterations described above, suggesting that the changes in the secretory cells of the experimental gland are related either directly or indirectly to the presence of 7,12-dimethylbenzo(a)anthracene; they may represent an initial event in carcinogenesis.

- 3069 ENHANCED REGRESSION OF DMBA-INDUCED MAMMARY CANCERS IN RATS BY COMBINATION OF ERGOCORNICINE WITH OVARECTOMY OR HIGH DOSES OF ESTROGEN. (E.) Quadri, S. K. (Dept. Physiol., Michigan State U., East Lansing), G. S. Kledzik and J. Meites. *Cancer Res* 34(3):499-501, 1974.

The effects of either ergocornine (EC), ovariectomy (Ovx), or high doses of estradiol benzoate (EB) alone, or combinations of EC and Ovx or EC and EB on growth of 7,12-dimethylbenzo(a)anthracene-induced mammary cancers were investigated in female Sprague-Dawley rats. After the cancers reached at least 1 cm in their largest diameter, the rats were ovariectomized or were given daily injections of EC (0.2 mg/100 g body weight) or EB (20 µg/rat) or were treated with combinations of EC and Ovx or EC and EB. By the end of 3 weeks, the combined treatments reduced mammary tumor size and number to a greater degree than any single treatment. The greater effectiveness of the combined treatments is believed to be due to the more complete inhibition of prolactin release produced by EC, together with the loss of estrogen resulting from Ovx or to the peripheral interference with prolactin action by high doses of EB.

3070 CELL-MEDIATED MUTAGENESIS OF MAMMALIAN CELLS WITH CHEMICAL CARCINOGENS. (E.) Huberman, E. (Weizmann Inst. Sci., Rehovoth, Israel) and L. Sachs. *Int J Cancer* 13(3):326-333, 1974.

A system of cell-mediated mutagenesis with carcinogenic hydrocarbons was developed by co-cultivating Chinese hamster V79 cells with lethally irradiated rodent cells that can metabolize chemically non-reactive carcinogens. The number of mutations achieved was dependent on the number of metabolizing cells. The carcinogens were not mutagenic when V79 cells were co-cultivated with nonmetabolizing cells. Inhibition of the hydrocarbon metabolizing enzymes by 7,8-benzoflavone inhibited mutagenicity. Cell-mediated mutagenicity was obtained with the carcinogenic hydrocarbons 7,12-dimethylbenz(a)anthracene, benzo(a)pyrene, and 3-methylcholanthrene. The most potent carcinogen, 7,12-dimethylbenz(a)anthracene, gave the highest frequency of mutations. No mutagenicity was obtained with the noncarcinogenic hydrocarbon benz(a)anthracene. This method detected mutagenicity with 0.1 µg/ml. These results clearly show a relation between the carcinogenicity of polycyclic hydrocarbons and their mutagenicity in this assay. Cell-mediated mutagenesis, when used with human cells, should be useful in testing for hazardous environmental chemicals which have to be metabolically activated to achieve mutagenesis.

3071 BENZO(a)PYRENE METABOLITES: EFFICIENT AND RAPID SEPARATION BY HIGH-PRESSURE LIQUID CHROMATOGRAPHY. (E.) Selkirk, J. K. (Nat'l. Cancer Inst., Bethesda, Md.), R. G. Croy and H. V. Gelboin. *Science* 184(4133):169-171, 1974.

High-pressure liquid chromatography constitutes an efficient, rapid, and reproducible method for the separation of the metabolites of benzo(a)pyrene. The metabolites were formed by incubation of (³H)- or (¹⁴C)-benzo(a)pyrene with liver microsomes prepared from rats which had been treated with methylcholanthrene. The 9,10-diol, 4,5-diol, and 7,8-diol were completely separated by liquid chromatography, whereas they are often incompletely resolved when thin-layer chromatography (TLC) is used. The 3-OH and 9-OH metabolites are not separable by TLC, while the single spot obtained from TLC is separated into two distinct peaks by liquid chromatography. The 1,6- and 3,6-quinones are completely separated from the phenols and diols, but are not entirely separated from each other. A third quinone not previously seen was tentatively identified as the 6,12-quinone.

3072 OXYGENATION OF BENZO(a)PYRENE IN A MODEL SYSTEM USING TRIFLUOROACETIC ACID AND HYDROGEN PEROXIDE. (E.) Ioki, Y. (Nat. Cancer Ctr. Res. Inst., Tokyo, Japan), M. Kodama, Y. Tagashir and C. Nagata. *Gann* 65(4):379-380, 1974.

The oxygenation of the carcinogen benzo(a)pyrene (BP) was studied in an *in vitro* model system using trifluoroacetic acid and hydrogen peroxide. Analy-

sis of the reaction products by electron spin resonance and fluorescence spectroscopy showed the presence in the benzene phase of the 6-oxy-BP radical, the same substance produced when BP is incubated with rat or mouse liver microsomal fractions. Fluorescence and excitation spectra of the water phase of alkaline extracts of the benzene phase showed that 3-hydroxy-BP was also formed in the reaction. This model system thus gives the same products as metabolites of arylhydrocarbon hydroxylase and may therefore be useful in studying the metabolism of BP.

3073 DISTRIBUTION AND METABOLISM OF BENZO(a)PYRENE IN FETAL MOUSE. (E.) Takahashi, G. (Chest Dis. Res. Inst., Kyoto U., Japan) *Bull Chest Dis Res Inst Kyoto Univ* 7(2):155-60, 1974.

The fetal and maternal somatic distribution as well as metabolism of radioactive benzo(a)pyrene (BP) were studied by autoradiography and chromatography in pregnant DDD strain mice injected i.v. on the 12th to 18th day of gestation. In pregnant females, BP was immediately distributed in the lungs and liver. After 5 hr, BP was most concentrated in lungs, liver, kidneys, intestine, bladder and gall bladder, adipose tissue, and mammary glands. BP was rarely found in muscle, brain and placenta. BP was also concentrated in fetal intestine, kidneys and liver with rare labeling of lungs, brain and other tissues, indicating that the fetus was able to metabolize and excrete the carcinogen. Chromatography of whole body and organ extracts from ³H-BP treated adults and fetuses revealed PB and three metabolites in the liver and kidneys. BP which appeared in excreta consisted only of conjugates with glucuronic and/or sulfuric acids. The conjugates in the bile were split into acids and hydroxy compounds which then appeared in feces of adults and fetuses near term.

3074 METABOLISM OF BENZ(a)ANTHRACENE EPOXIDES BY RAT-LIVER. (E.) Booth, J. (Inst. Cancer Res., London, England) and P. Sims. *Biochem Pharmacol* 23(18):2547-2555, 1974.

Previous studies have shown that benz(a)anthracene (BA) is metabolized to 5,6-dihydro-5,6-dihydroxybenz(a)anthracene and 8,9-dihydro-8,9-dihydroxybenz(a)anthracene at similar rates by a rat liver microsomal fraction with NADPH. When the soluble liver fraction and glutathione (GSH) are added to the reaction mixture, the rate of formation of the 5,6-isomer is greatly reduced while that of the 8,9-dihydrodiol is unaffected. The present study was undertaken to investigate the further metabolism of the two reaction intermediates, BA5,6- and BA8,9-oxide, into dihydrodiols and into reduced glutathione (GSH) conjugates in the rat liver microsomal system. Reaction products were identified by thin-layer chromatography. Each epoxide intermediate was metabolized to a dihydrodiol by microsomal "epoxide

hydrazase" at a similar rate. However, conjugation with GSH, a reaction mediated by "glutathione S-epoxide transferase" in the soluble liver fraction, proceeded more rapidly with the 5,6- than with the 8,9-isomer. When the two BA epoxides were incubated with both enzymes, a situation where there was competition for the substrates, the 5,6-isomer was primarily converted to the GSH conjugate by "GSH transferase", whereas the 8,9-isomer was mainly converted to the dihydrodiol by "epoxide hydrazase".

3075 EFFECT OF β -IRRADIATION ON 3-METHYLCHOLANTHRENE INDUCTION OF BRAIN TUMORS IN MICE.

(E.) Mandybur, T. I. (U. Cincinnati Coll. Med., Ohio). *J Natl Cancer Inst* 53(2):399-406, 1974.

Localized radiation was delivered to the brains of C57BL mice by implanted β -ray-emitting tungsten wires. Mice were divided into four groups given 1000, 2400, 3900, and 5000 rad, resp.; 3-methylcholanthrene (MCA, 2 mg) was then implanted into the irradiated brain. Control animals receiving only radiation had no tumors. When MCA implantation was preceded by β -radiation, tumor yield was inversely proportional to the radiation dose. Irradiation apparently decreased the neoplastic response of the nervous tissue by reducing the number of cells available to be stimulated by MCA. The latent period of tumorigenesis and histologic types of neoplasms developing in irradiated brain tissue were comparable to those in a nonirradiated group into which MCA pellets were implanted at a similar location.

3076 INHIBITION OF THE EFFECTS OF METHYLCHOLANTHRENE ON MOUSE PROSTATE IN ORGAN CULTURE BY VITAMIN A AND ITS ANALOGS. (E.) Lasnitzki, H. (Strangeways Res. Lab., Cambridge, England) and D. S. Goodman. *Cancer Res* 34(7):1564-1571, 1974.

Four vitamin A analogs (retinol, retinoic acid, α -retinoic acid, and a cyclopentyl analog, R08-7699) were studied for their effect on methylcholanthrene (MCA)-induced hyperplasia and squamous metaplasia of inbred R mouse prostate glands in 7-9 day old organ cultures. MCA (4 μ g/ml) alone stimulated the alveolar epithelium to become hyperplastic and undergo squamous metaplasia and parakeratosis. Addition of each of the vitamin A analogs (0.3-3.0 μ g/ml) to MCA-treated prostate cultures effectively prevented the MCA-induced changes. Since α -retinoic acid and R08-7699 have little or no growth-promoting biologic activity and still prevented the effects of MCA, the anticarcinogenic activity of vitamin A was not correlated with its biologic activity. Studies with 3 H-MCA showed that retinoic acid had no effect on cellular uptake or release of MCA. Sodium dodecyl sulfate also had no effect on the action of MCA. These findings suggested that the effects of vitamin A were not due to its surface-active properties. Retinoic acid alone had no effect on thymidine incorporation into mouse prostate cultures, as determined autoradiographically, but did partially inhibit the stimulation of 3 H-thymidine uptake by MCA.

3077 THE RELATIVE CARCINOGENIC ACTIVITIES OF A SERIES OF 5-METHYLCHRYSENE DERIVATIVES.

(E.) Coombs, M. M. (Imp. Cancer Res. Fund, London, England), T. S. Bhatt, M. Hall and C. J. Croft. *Cancer Res* 34(6):1315-1318, 1974.

The carcinogenicity of 1,11-dimethylchrysene (\approx 5,7-dimethylchrysene) and its 1,2,3,4-tetrahydro-, 3,4-dihydro-, and 1,2,3,4-tetrahydro-1-oxo derivatives was tested by mouse skin painting. Male and female mice each received 30 μ g of the chrysene on the dorsal skin twice weekly for one yr. All animals were observed for a second yr and were sacrificed for histologic examination when their tumors reached 8-10 mm diameter. Of the chrysenes tested, the 1-ketone was the most active, producing tumors in 17 of 20 mice alive at the time the first tumor appeared (mean latent period of 55 wk). The dimethyl and dihydro derivatives were intermediate in activity. The results indicated that the size of the 4th, partially saturating ring, has little influence on the relative carcinogenicity of the ketones and tetrahydrocarbons. This is not the case for the dihydrocarbons.

3078 CARCINOGENIC EFFECT OF DIBUTYLNITROSAMINE IN EUROPEAN HAMSTERS (*CRICETUS CRICETUS*). (E.) Althoff, J. (Med. Coll., Hannover, W. Germany), U. Mohr, N. Page and G. Reznik. *J Natl Cancer Inst* 53(3):795-800, 1974.

Captured European hamsters (*Cricetus cricetus*) were treated s.c. with *N*-dibutyl nitrosamine (DBN) at various dose levels. The LD₅₀ was 2462 mg/kg in males and 1866 mg/kg in females. All animals surviving more than 20 wk developed tumors in more than one organ. The effects of DBN were dose-dependent. Most neoplasms were found in the respiratory tract. Papillary polyps, papillomas, squamous cell carcinomas, and one adenocarcinoma were found in the nasal cavities, while mixed-cell carcinomas and a few adenocarcinomas were found in the lungs. In addition, a transitional cell carcinoma (primary tumor in the urinary bladder) metastasized into the lung. Most animals developed papillomas of the forestomach. The second largest number of tumors was found in the urinary bladder; these were transitional cell papillomas, carcinomas, and squamous cell carcinomas.

3079 EFFECT OF CYCLOPROPENOID COMPOUNDS ON THE CARCINOGENIC ACTIVITY OF DIETHYLNITROSAMINE AND AFLATOXIN B₁ IN RATS. (E.) Nixon, J. E. (Dept. Food Sci. Technol., Oregon State U., Corvallis), R. O. Sinnhuber, D. J. Lee, M. K. Landers and J. R. Harr. *J Natl Cancer Inst* 53(2):453-458, 1974.

The cocarcinogenic activity of cyclopropenoid fatty acids (CPFA) was investigated in Wistar and Fischer rats fed food-grade cottonseed oil (0.35% CPFA) or *Sterculia foetida* oil (50% CPFA) with aflatoxin B₁ or diethylnitrosamine (DEN). Wistar rats fed 0.2 or 1.0 mg/kg DEN daily for an average of 7-14 months developed hepatomas with incidence rates of 40 and

70%, resp.; they developed no other tumors. Wistar rats fed 20 or 100 ppb aflatoxin B₁ showed hepatoma incidence rates of 0 and 43%, resp., and total tumor incidence rates of 10 and 51%, resp. The hepatoma incidence increased from 41 to 61% in male Wistar rats when CPFA was added to the 100 ppb aflatoxin B₁ diets, but incidences were only 4 and 14% when CPFA was added to the low and high level DEN diets, resp. Fischer rats fed 0.1 mg/kg DEN were free of other tumors, but 7% developed hepatomas; when CPFA was added to the diet, 10% developed other tumors. The Fischer rats were more sensitive to 20 ppb aflatoxin B₁ than the Wistar rats (hepatoma incidence of 21 vs 0%). The incidence of kidney tumors was less than 0.3% in all rats. CPFA exhibited a weak cocarcinogenic effect in specific comparisons, but generally did not influence the carcinogenicity of aflatoxin B₁ or DEN.

3080 TUMORIGENESIS IN THE NASAL OLFACTORY REGION OF SYRIAN GOLDEN HAMSTERS AS A RESULT OF DI-*n*-PROPYLNITROSAMINE AND RELATED COMPOUNDS. (E.) Pour, P. (U. Nebraska Med. Ctr., Omaha), A. Cardesa, J. Althoff and U. Mohr. *Cancer Res* 34(1):16-26, 1974.

The morphology of neoplasms in the nasal olfactory region of the Syrian golden hamster observed after weekly s.c. injections for life of di-*n*-propylnitrosamine (3.75, 7.5, 15, 30, and 60 mg/kg), β-hydroxy-propyl-*n*-propylnitrosamine (37.5, 75, and 150 mg/kg), β-oxopropyl-*n*-propylnitrosamine (30, 60, and 120 mg/kg), and methyl-*n*-propylnitrosamine (12.5, 25, and 50 mg/kg), are described; all four compounds induced tumors. Neoplastic lesions were characterized by the proliferation of three often intermingled cell types (large cuboidal, cylindrical, and small cell). These cells were similar to cells of olfactory glands, sustentacular cells, and basal cells. Neurogenic elements were not identified in the tumors. These neoplasms were thus felt to originate in the olfactory epithelium.

3081 DIBENAMINE: SELECTIVE PROTECTION AGAINST DIETHYLNITROSAMINE-INDUCED HEPATIC CARCINOGENESIS BUT NOT ORAL, PHARYNGEAL AND ESOPHAGEAL CARCINOGENESIS. (E.) Weisburger, E. K. (Carcinogen Metabolism Toxicol. Br., Natl. Cancer Inst., Bethesda, Md.), J. M. Ward and C. A. Brown. *Toxicol Appl Pharmacol* 28(3):477-488, 1974.

Six-wk-old male Fischer rats were given 40 ppm diethylnitrosamine (DEN) in their drinking water for 10 wk. During this period they were injected thrice weekly with dibenamine (DBA) (12.5 or 25 mg/kg s.c.). Non-DEN-treated controls were also injected thrice weekly with 12.5 or 25 mg/kg dibenamine for 10 wk. Virtually all of the DEN-treated rats developed tumors of the oral cavity, pharynx, and esophagus, the number and distribution of these tumors being unaffected by the presence, absence, or dose level of DBA. None of the rats treated with DBA alone de-

veloped oral, pharyngeal, or esophageal neoplasms. The DBA-injected animals exposed to DEN had lower liver wt, the degree of protection being related to the dose of DBA. Grossly, the livers of the DEN-treated animals were the most severely affected. Generally, the left and median lobes were greatly enlarged and contained several irregularly shaped carcinomas; other lobes were less frequently involved. Small round nodules were seen in most livers. DBA significantly protected the DEN-treated rats from liver tumors, the protective effect being dose related. The number of pulmonary metastases was also inversely related to the dose of DBA. A few of the rats injected with DBA developed tumors at the site of injection and one animal developed an intestinal tumor. Thus, DBA may itself be a carcinogen.

3082 STUDIES ON THE ROLE OF STIMULATED EPIDERMAL DNA SYNTHESIS IN THE INITIATION OF SKIN TUMORS IN MICE BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Bowden, G. T. (Med. Ctr., U. Wisconsin, Madison) and R. K. Boutwell. *Cancer Res* 34(7):1552-1563, 1974.

The role of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) on initiation of skin tumors in female CD1 mice was studied following stimulation of epidermal DNA synthesis by application of a single topical dose of 0.5% croton oil. Maximum epidermal DNA synthesis occurred 18 hr after application of croton oil. Topical application of 1 or 5 μM MNNG after croton oil treatment followed by twice-weekly application of 0.25% croton oil produced a three- to four-fold increase in papilloma production when compared to a control group pretreated with acetone. Studies using ³H-MNNG showed no difference between acetone and croton oil-pretreated groups in the extent of MNNG binding to epidermal cell protein, RNA, or DNA. Chromatographic analysis of ³H-MNNG labeled DNA hydrolysates from acetone and croton oil-pretreated animals showed the same positions and extent of methylation of DNA bases (*N*-7-guanine, *O*-6-guanine, and *N*-3-adenine). There was no difference in the extent of binding of H-MNNG to replicating and nonreplicating DNA from epidermal cells of croton oil-pretreated mice.

3083 COLON CARCINOGENESIS IN GERM-FREE RATS WITH 1,2-DIMETHYLHYDRAZINE AND *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Reddy, B. S. (Naylor Dana Inst. Dis. Prevention, Am. Health Fdn., New York, N.Y.), J. H. Weisburger, T. Narisawa and E. L. Wynder. *Cancer Res* 34(9):2368-2372, 1974.

The effect of intestinal microflora on the sensitivity of the colon to the carcinogenic effect of 1,2-dimethylhydrazine (DMH), which needs metabolic activation, and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine a direct-acting carcinogen, was studied using Fischer germ-free and conventional female rats.

None of the germ-free rats that received s.c. injections of DMH (10 mg/wk/kg for 20 wk) showed colon tumors, whereas 17% of the conventional rats treated similarly developed adenocarcinomas of the colon. At 20 wk after the last injection of DMH, 11% of the germ-free rats developed adenomas, whereas 25% of the conventional rats showed colonic tumors, 67% of which were adenocarcinomas and 34% of which were adenomas. In contrast to DMH, intrarectal injection of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (total dose, 48 mg in 20 wk) nearly doubled the multiple colonic tumors in germ-free rats compared to conventional controls. It is concluded that the intestinal microflora play a modifying role in colon carcinogenesis by DMH.

3084 CELL CYCLE DEPENDENCY OF ONCOGENIC TRANSFORMATION INDUCED BY *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE IN CULTURE. (E.) Bertram, J. S. (Med. Sch. U. Wisconsin, Madison) and C. Heidelberger. *Cancer Res* 34(3):526-537, 1974.

Malignant transformation was induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in synchronized cultures of the C3H/10T1/2 CL8 line of mouse fibroblasts. Cells were synchronized by arginine or isoleucine deprivation for 48 hr, by 2mM thymidine for 24 hr, or by release from postconfluence inhibition of cell division. Replicate cultures were treated with MNNG (4 µg/ml) at various times prior to, at, or after release of the block. DNA synthesis, as determined by ³H-thymidine uptake, began 4 hr after release of cells from arginine or isoleucine deprivation, and about 90% of the cells doubled after 10-14 hr. A peak in transformation frequency (TF) occurred at the time of release in arginine-deprived cells, and 4 hr after release of the block in isoleucine-deprived cells. Synchrony induced by 2 mM thymidine was poorly defined; DNA synthesis began within 2 hr and cell division began within 4 hr after removal of the thymidine. The peak in TF occurred at the time of release of the block. When cells were released from postconfluence inhibition of cell division, a peak of TF was observed 4 hr prior to S phase, and a second peak of TF was located shortly before the second round of DNA synthesis. MNNG killed 99.9% of cells at the time of maximal TF, and toxicity increased as cells entered S phase. Arginine deprivation did not cause an alteration in chromosome number. Morphologically transformed colonies from MNNG-treated dishes were cloned, cultured, and injected s.c. into X-irradiated syngeneic mice. Nine of 10 transformed lines gave sarcomas, but the untreated line did not.

3085 CELL CYCLE DEPENDENCY OF DNA DAMAGE AND REPAIR IN TRANSFORMABLE MOUSE FIBROBLASTS TREATED WITH *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Peterson, A. R. (U. Wisconsin Med. Sch., Madison), J. S. Bertram and C. Heidelberger. *Cancer Res* 34(7):1600-1607, 1974.

The effects of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) on DNA damage and repair were studied by al-

kaline sucrose gradient sedimentation in transformable C3H/10T1/2 CL8 mouse fibroblasts synchronized by arginine deprivation. Cells were treated for 4 hr with MNNG (varying conc. or 0.5 µg/ml) beginning 4 hr before, at the time of, or 4 hr after release from arginine deprivation. Labeling with ¹⁴C-thymidine showed that the first wave of DNA synthesis occurred about 4 hr after release, reached a maximum 9 hr after release, and declined to a minimum 14 hr after release. DNA repair occurred rapidly in cells treated with MNNG 4 hr before or shortly after the initiation of DNA synthesis. In cells treated with MNNG at the time DNA synthesis was blocked, DNA repair did not occur until the cells were released from the block. MNNG was most lethal to cells treated shortly after commencement of DNA synthesis. Cells treated either 4 hr before initiation of DNA synthesis or while DNA synthesis was blocked were less, but equally susceptible to the lethal effects of MNNG. This pattern did not conform to the pattern of susceptibility to MNNG-induced transformation which was greatest 4 hr before initiation of DNA synthesis. It was thus concluded that in this system there was no direct correlation between DNA repair and susceptibility to transformation or lethal effect by MNNG.

3086 COMBINED EFFECT OF VARIOUS SURFACTANTS ON GASTRIC CARCINOGENESIS IN RATS TREATED WITH *N*-METHYL-*N'*-NITRO-*N*-NITROSOGUANIDINE. (E.) Fukushima, S. (Nagoya City U. Med. Sch., Japan), M. Tatematsu and M. Takahashi. *Gann* 65(4):371-376, 1974.

The effects of various nonionic and ionic surfactants commonly used in commercial products on the induction of cancers of the glandular stomach by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) were studied in male Wistar rats. Groups of 9 or 10 rats were given drinking water *ad lib* for 26-30 wk containing 50 mg/liter MNNG alone or in combination with one of various nonionic (Tween 20, 40, 60 or 80, 0.4%) or ionic (Span 20, 0.3%, glyceryl monosterate, 2%, sucrose monopalmitate, 0.2%, sodium N-lauryl sulfate, 0.25% sodium N-lauryl sarcosinate, 0.5%) surfactants. Autopsies were performed after 80 wk or when animals died. All groups which received MNNG plus detergent (except those receiving Tween 80) had a higher incidence of tumors of the glandular stomach (56-90%) than did the controls which received only MNNG (50%). Grossly, most tumors were localized to the pyloric region. Histologically, most tumors were well-differentiated adenocarcinomas which tended to infiltrate but did not metastasize. All but three of the surfactant-treated groups also had one or two undifferentiated adenocarcinomas and all but four of these groups also had from one to four sarcomas (fibrosarcoma, hemangiosarcoma, osteogenic or undifferentiated sarcoma). None of the animals treated with MNNG alone developed undifferentiated adenocarcinoma or sarcoma. These results suggest that surfactants may promote absorption of MNNG from the glandular stomach and may increase the activity of harmful chemical substances in the environment.

3087 EFFECTS OF KIDNEY AND PANCREAS TRANSPLANTATION ON STREPTOZOTOCIN-INDUCED MALIGNANT KIDNEY TUMORS IN RATS. (E.) Mauer, S. M. (Univ. Minnesota Med. Sch., Minneapolis), D. E. R. Sutherland, M. W. Steffes, C. S. Lee, J. S. Najarian and D. M. Brown. *Cancer Res* 34(7):1643-1645, 1974.

The effects of kidney and pancreas transplantation on the development of malignant kidney tumors were studied in highly inbred Lewis male and female rats rendered diabetic by a single i.v. injection of streptozotocin (65 mg/kg), a N-nitrosomethylamide previously shown to induce renal tumors in rats. No animals had evidence of renal tumors six months after streptozotocin injection, when all were chronically diabetic. At this time, kidneys were transplanted from diabetic donors into normal, unilaterally nephrectomized recipients. Four of these transplanted kidneys developed renal tumors within the next four months. Three of 10 diabetic animals receiving normal kidneys developed tumors involving their own remaining kidney within the next four months. Kidneys transplanted from normal donors into normal or diabetic animals did not develop tumors. Four of nine rats developed renal tumors within six months following reversal of their diabetic state by successful transplantation of pancreatic tissue from normal donors. These studies suggested that streptozotocin-induced renal tumors in rats are due to a direct effect on the kidney rather than to the diabetic state.

3088 PROMOTION OF MAMMARY CARCINOGENESIS AND LEUKEMOGENIC ACTION BY PHORBOL IN VIRGIN FEMALE WISTAR RATS. (E.) Armuth, V. (Weizmann Inst. Sci., Rehovot, Israel) and I. Berenblum. *Cancer Res* 34(10):2704-2707, 1974.

The effects of phorbol administration on leukemogenesis and on 7,12-dimethylbenz(a)anthracene (DMBA)-induced mammary carcinoma were studied in virgin female Wistar rats. Animals received either phorbol alone (2 ml of 0.2% i.p. twice weekly for 9 months), DMBA alone (0.25, 2, or 6 mg as a single feeding), or DMBA followed in one wk by phorbol injections (twice weekly for 10 wk). The lowest DMBA dose (0.25 mg), alone or with phorbol, failed to induce mammary tumors. The differences in mammary tumor incidence between rats given 2 mg DMBA alone (3% of 35) or DMBA followed by phorbol (21% of 34) were insignificant. However, rats treated with 6 mg DMBA and phorbol developed significantly more mammary tumors (78% of 36) than did rats which received only 6 mg DMBA (21% of 39). Spontaneous mammary tumor incidence in untreated controls was 18%. All tumors were well-differentiated adenocarcinomas. Rats treated with phorbol alone showed an unusually high (94%) incidence of lymphatic leukemia with a latent period of 299 ± 22 days compared with incidences and latent periods of only 23% and 39% and 152 ± 21 days and 127 ± 16 days for animals receiving 2 and 6 mg DMBA, resp., plus phorbol. DMBA alone was not leukemogenic and leukemia occurred in only 2% of untreated controls. The thymus was involved in every case. These results indicate that mammary carcinogenesis may be promoted in rats by nonhormonal substances. The shorter la-

tent periods for leukemogenesis in rats given DMBA plus phorbol implicate some type of cocarcinogenic action.

3089 ACTION OF 4-NITROQUINOLINE 1-OXIDE ON MITOCHONDRIAL DNA IN YEAST. (E.) Morita, T. (Shizuoka Coll. Pharmacy, Japan) and I. Mifuchi. *Cann* 65(1):27-32, 1974.

The action of 4-nitroquinoline 1-oxide (4-NQO) on yeast mitochondrial DNA was studied using synchronous cell cultures of the diploid yeast *Saccharomyces cerevisiae* IFO-0209 and the respiration-deficient (RD) mutant strain N-1. Aliquots of these cultures were treated with 1.9 μ g/ml of 4-NQO for 5 min at 30 C. The induction of RD mutation by 4-NQO was significantly correlated with the division cycle of the yeast cells, the induction rate of RD mutants reaching a maximum about 5 min prior to doubling of the cell number. At the same point in the cell cycle, the number of mitochondria in ultrathin sections of synchronously growing yeast cells reached a maximum. Similarly, the activity of respiratory enzymes such as succinic dehydrogenase, succinic-cytochrome c reductase, and NADH-cytochrome c reductase reached peak levels immediately before the stepwise increase of the cell number. Hydroxyapatite column chromatography of DNA preparations from intact 4-NQO-induced RD mutants and their mitochondrial fractions indicated that mitochondrial DNA had disappeared from the mutant cells. Thus, the target of 4-NQO in the induction of RD mutation appears to be the mitochondrial DNA.

3090 UROEPITHELIAL TUMORS OF THE RENAL PELVIS ASSOCIATED WITH ABUSE OF PHENACETIN-CONTAINING ANALGESICS. (E.) Johansson, S. (Sahlgren's Hosp., U. Goteborg, Sweden), L. Angervall, U. Bengtsson and L. Wahlqvist. *Cancer* 33(3):743-753, 1973.

This is a review of 62 patients with abuse of acetophenetidin-containing drugs and uroepithelial tumors of the renal pelvis. Most of the patients had a preexisting nephropathy with papillary necrosis as a prominent feature. Fifty-six per cent of the patients have died, most of them from the tumor disease, but many were uremic at the time of death. Thus, the coexisting nephropathy contributed to the poor prognosis. The risk of overlooking an early tumor diagnosis is emphasized. The diagnosis of a uroepithelial tumor of the renal pelvis should always lead to an analysis of the analgesic consumption, besides looking for occupational factors. On the basis of present knowledge of urinary tract carcinogens and acetophenetidin metabolites it is assumed that acetophenetidin is the crucial factor for the development of uroepithelial tumors in this study.

- 3091 STERIC EFFECTS IN THE NITROSATION OF PIPERIDINES. (E.) Jones, A. R. (Oak Ridge Natl. Lab., Tenn.), W. Liĳinsky and G. M. Singer. *Cancer Res* 34(5):1079-1081, 1974.

The rates of nitrosation of four methyl-substituted piperidines by reaction with nitrous acid to form the corresponding N-nitrosopiperidines were studied and compared to the rate of nitrosation of piperidine. Reaction products were identified and quantitated by gas chromatography. The relative rates of nitrosation of piperidine, 2-methylpiperidine, 2,6-dimethylpiperidine and 2,2,6,6-tetramethylpiperidine were approximately 100:20:10:1. There thus appeared to be considerable steric hindrance to nitrosation of the amine by the presence of as little as one methyl group adjacent to the nitrogen atom. The reaction rate of N-methylpiperidine was at least 10,000 times slower than that of piperidine. There was considerable increase in the reaction rate of N-methylpiperidine with an increasing ratio of nitrite to amine. It was concluded, therefore, that the greatest risk of formation of carcinogenic amines following ingestion by humans is from unhindered, relatively weakly basic secondary amines from N-nitroso derivatives.

- 3092 CARCINOGENICITY OF POTASSIUM 1-METHYL-7-[2-(5-NITRO-2-FURYL)VINYL]-4-OXO-1,4-DIHYDRO-1,8-NAPHTHYRIDINE-3-CARBOXYLATE IN ICR MICE. (E.) Kanisawa, M. (Inst. Food Microbiol., Cuba U., Japan), H. Katoh and K. Aiso. *Gann* 65(1):1-11, 1974.

The carcinogenic activities of potassium 1-methyl-7-[2-(5-nitro-2-furyl)vinyl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (NFN) and 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (nalidixic acid) were examined histopathologically using 134 ICR/JCL mice. NFN (0.02% by weight) was fed to 60 animals (Group A) for 9 wk, after which the animals were returned to the basal diet for 5 wk. NFN (0.01%) was again fed for 7 wk, after which the animals were returned to the basal diet for 15 wk. Controls were maintained on the basal diet for 36 wk. An additional group (B) was fed NFN (0.015%) for 26 wk, followed by 10 wk on the basal diet. Papillary growths with hyperkeratosis in the squamous epithelium of the forestomach were observed in most of the NFN-treated mice. Squamous cell carcinomas of the forestomach were induced in one male and five females in the Group A animals surviving at least 31 wk, but no tumors developed in the glandular stomach. Pulmonary adenomas, often multifocal, were induced in 19 mice after 21 wk. Other tumors included one lymphatic leukemia, one subcutaneous fibroma, and one uterine myosarcoma in Group A, and one squamous cell carcinoma of the forestomach, eight lung adenomas, two lung adenocarcinomas, and two lymphatic leukemias among the 10 Group B mice surviving at least 16 wk. One pulmonary adenoma and one lymphatic leukemia were found in the control group. Nalidixic acid (0.05%) was fed to 20 mice for 36 wk; the only tumorigenic alteration was one hepatic adenoma.

- 3093 URINARY EXCRETION OF METHYLATED PURINES FOLLOWING INHALATION OF DIMETHYL SULPHATE. (E.) Lofroth, G. (Radiobiol. Dept., U. Stockholm, Sweden), S. Osterman-Golkar and R. Wennerberg. *Experientia* 30(6):641-642, 1974.

Inhalation tests were performed with ^3H -dimethyl sulfide (DMA, 150 mC/mM) in male NMRI mice and the quantity of methylated purines subsequently excreted in the urine determined. Although the estimation of the total dose, assuming a standard breathing, may involve a considerable error, the data indicate that the major part of the ^3H -activity of DMS is excreted in the urine within the first 48 hr after exposure. In addition to 7-methylguanine, (7 MeGua), the presence of two minor products, 1-methyladenine (1 MeAde) and 3-methyladenine (3 MeAde), was also detected in the urine. The excretion rate of 7 MeGua is rapid, having an apparent $t_{1/2}$ of about 1 day. The results indicate that 1 MeAde and 3 MeAde are excreted faster than 7 MeGua. The total amount of urinary methylated purines originated from the methylation of nucleic acid constituents by DMS is of the order of 0.15 to 0.3% of the dose. There is only a small dose dependence, since a decrease of the dose by a factor of about 100 only decreases the relative amount of methylated purines by a factor of two.

- 3094 RAUWOLFIA DERIVATIVES AND CANCER. (E.) Immich, H. (Dept. Med. Doc. Stat., Heidelberg U., W. Germany). *Lancet* 7883:774-775, 1974.

The results of three previous publications in which it was concluded that women who take rauwolfia derivative (reserpine) have an increased risk of developing breast cancer are refuted. It is pointed out that in all three studies the authors selected their control groups in such a way that the users of rauwolfia derivatives in those groups were grossly underrepresented, resulting in a falsely low risk factor for this group. In addition, it is further stated that the authors did not take into account the different age distributions of "users" and "nonusers", resulting in an inhomogeneity between the groups with this respect. The high rate of rauwolfia derivative use in the over-60 population is a result of the higher probability of developing hypertension in this group. The higher probability of developing breast cancer in this group, which is of the same order as that for developing hypertension, is thus only a coincidental association.

- 3095 PRENATAL INDUCTION OF NEUROGENIC TUMORS IN HAMSTERS BY PRECURSORS ETHYLUREA AND SODIUM NITRITE. (E.) Rustia, M. (U. Nebraska Med. Ctr., Omaha) and P. Shubik. *J Natl Cancer Inst* 52(2):605-607, 1974.

Beginning on day 12 of gestation, eight pregnant Syrian golden hamsters were given four consecutive daily doses of ethylurea (100 mg/kg) and sodium

nitrite (50 mg/kg) administered simultaneously by intragastric intubation. The female progeny had a high incidence of neurogenic tumors (69%) in the peripheral nervous system (PNS), with an average latent period of 40 wk. The males had a significantly lower incidence of PNS tumors (12.5%), and tumor-bearing males tended to have only one tumor compared with multiple tumors in the tumor-bearing females. No tumors were seen in the exposed mothers. Ther nerve sheath tumors developed more frequently from the spinal nerves than from the cranial nerves. Metastases were never observed. The cells of the neoplasms resembled Schwann cell elements. Most of the tumors were considered malignant neurinomas, although benign neurinomas and neurofibromas were also seen. The data strongly suggest an influence of estrogenic hormones on the development and growth of these neoplasms.

- 3096 EXPERIMENTAL EPENDYMONAS: *IN VIVO* AND *IN VITRO* MORPHOLOGY. (E.) Mennel, H. D. (Max Planck Inst. Brain Res., Cologne, W. Germany) and J. Bucheler. *Z Krebsforsch* 82(1):65-74, 1974.

Four primary tumors of rats diagnosed as ependymomas were explanted *in vitro* and transplanted into isogenic hosts. The tumors were induced mainly in transplacental experiments with N-ethyl-N-nitrosourea in rats combined with administration of estrogen. Transplanted tumors grew in the brain of the grafted animals within and in the border zone of the ventricles. Tumors *in vitro*, primary as well as transplanted, had uniform cellular components forming a dense network of bipolar and stellate single cells. The *in vitro* movement took place along and inside the filamentous protoplasmic processes. These investigations show that the ventricular border zone not only plays a role in the formation of the original tumors but also in the growth of the transplanted tumors.

- 3097 EFFECT OF URETHAN, N-HYDROXY URETHAN AND URETHAN-DNA COMPLEX ON DNASE ACTIVITY OF MOUSE CELLS *IN VITRO*. (E.) Talageri, V. R. (Cancer Res. Inst., Bombay, India) and S. V. Bhide. *Indian J Cancer* 11(2):129-133, 1974.

DNase activity was determined photometrically in Swiss mouse fibrosarcoma cells, in untreated cells of newborn mouse thigh muscle, and in thigh muscle cells exposed for 72 hours to urethan, N-hydroxyurethan, urethan-liver cell DNA complex (Ur-DNA), or calf-thymus DNA. The presence of DNA as calf-thymus DNA or as Ur-DNA in the culture medium led to significant increases in the DNase activity, whereas urethan and N-hydroxy urethan had no appreciable effect on enzyme activity. The increase in DNase activity could be blocked almost completely by the addition of endoxan, a protein synthesis inhibitor, suggesting that the observed increase in DNase activity may be due to the induced enzyme synthesis rather than activation of the enzyme. Enzyme levels were significantly lower in untreated tumor cells than in the normal untreated cells.

- 3098 DEVELOPMENT OF BROAD SPECTRUM OF TUMORS BY ETHYLNITROSUREA IN MICE AND THE MODIFYING ROLE OF AGE, SEX, AND STRAIN. (E.) Vesselinovetch, S. D. (Pritzker Sch. Med., U. Chicago, Ill.), K. V. N. Rao, N. Mihailovich, J. M. Rice and L. S. Lombard. *Cancer Res* 2530-2538, 1974.

The modifying roles of age, sex, and strain on the incidence, multiplicity, and spectrum of tumors induced by ethylnitrosourea (ENU) were studies in F₁ hybrids of C57BL/6J x C3HeB/FeJ and C3HeB/FeJ x A/J mice of both sexes which were given single i.p. injections (60 or 120 µg/gm) of ENU at 1, 15, or 42 days of age. ENU-injected animals generally died by the 90th wk of age due to tumor which involved primarily the lung, liver, Harderian glands, stomach, ovaries, lymphoreticular system, kidneys, mammary gland, uterus, or nervous system. The age at the time of ENU injection was a major factor in modifying neoplastic response with 1) animals injected as newborns or infants (15 days) developing significantly more liver, kidney, and ovarian tumors than animals injected as adults (42 days); 2) animals injected as infants or adults having more stomach and lymphoreticular system tumors than mice injected as newborns; and 3) animals injected as adults having more lung, Harderian gland, and mammary gland tumors than mice injected as either newborns or infants. Males developed significantly more liver and Harderian gland tumors than females and females developed more lymphoreticular and mammary neoplasms than males. C57/BL/6J x C3HeB/FeJ F₁ mice were more susceptible to development of liver, Harderian gland, lymphoreticular, ovarian, and mammary gland tumors; C3HeB/FeJ x A/J F₁ mice developed more lung tumors. Thus, age, sex, and genetic background of an experimental animal must be considered when studying mechanisms of carcinogenesis in a given tissue or of a given substance.

- 3099 AN ANALYSIS OF THE CHANGING URETHAN RESPONSE OF THE DEVELOPING MOUSE EMBRYO IN RELATION TO MORTALITY, MALFORMATION, AND NEOPLASM. (E.) Nomura, T. (Osaka U. Med. Sch., Japan). *Cancer Res* 34(9):2217-2231, 1974.

Urethan (0.2-1.5 mg/g was given to pregnant ICR/Id mice on days 3-19 of gestation, and a quantitative analysis of the changing urethan response of the developing mouse embryo in relation to mortality, growth inhibition, malformation, and neoplasm was investigated, utilizing the fast action and unrestricted placental penetration of urethan. When urethan was given before implantation on day 3, preimplantation loss was observed. The treatment with urethan (1.5 mg/g) just after implantation on day 7 caused complete resorption of the embryo. Early deaths were observed only when 1.5 mg/g were given on day 8, and late deaths were observed on days 8-11. Occurrence of malformation in an organ was confined to organs exposed at the very early stage of their organogenesis. Lung anomaly was induced at its maximum when 1.5 mg/g were given on day 9, and liver anomaly peaked on day 8. These stages corresponded to the time of differentiation of these fetal organs. The incidence of embryonic deaths

and malformations by urethan showed a sharp threshold dose; it dropped from 93 to 34% at 1.5 mg urethan/g to virtually zero at 1.0 mg/g. This is in striking contrast to the finding that tumors are induced in lung and liver when urethan is given during late organogenesis and fetal growth of each organ, even when very small amounts (0.2 mg) are given. Growth inhibition of fetal organs was observed when urethan was given during organogenesis and the early stage of fetal growth. The time of differentiation was most sensitive to small amounts of urethan (0.5 mg).

3100 METABOLISM OF URETHANE AND ITS INTERACTION WITH NUCLEIC ACIDS AND PROTEINS. (E.)

Prodi, G. (Cancer Inst., U. Bologna, Italy), P. Rocchi, S. Grilli and A. M. Ferreri. *Ital J Biochem* 22(5-6):203-216, 1974.

DNA, rRNA, nuclear proteins, and cytoplasmic proteins were extracted from normal and regenerating Wistar rat liver 24 hr after the i.p. administration of labeled urethane or ethanol. The radioactivity bound to DNA after ethanol administration was negligible in normal liver and significant in regenerating liver, although 10-fold lower than DNA activity of regenerating liver after injection of the same dose of urethane. After urethane administration, DNA labeling of regenerating liver was 6-fold higher than that of normal liver, indicating that the amount of binding between urethane metabolites and nucleic acids depends on DNA synthesis. To further study urethane metabolism, perchloric-soluble materials from the pooled livers of treated rats were separated on Dowex 50-X8 columns and the UV absorption of radioactive peaks measured at 260 nm. The material from urethane-treated rats contained two compounds which were not present in the same material from ethanol-treated rats. The molecular wt of the two compounds (2800 and 1500) makes it unlikely that they are active metabolites; rather they may represent two perchloric-soluble products of interaction with the active metabolites. *In vivo* studies of the effect of ethanol on urethane metabolism revealed that ethanol inhibits the first step of urethane metabolism which leads to N-hydroxyurethane, and that the presence of ethanol (unlabeled) results in prolonged elevation of serum urethane (labeled) levels. To determine if the latter effect involved higher binding to nucleic acids, hepatectomized rats were injected i.m. with unlabeled ethanol before and after i.p. injection of labeled urethane. The specific activity of DNA isolated from the liver 24 hr after urethane administration was 64 dpm/mg compared with the 619 dpm/mg measured in regenerating liver after administration of urethane alone. Thus, ethanol prevents urethane metabolism and any interaction with the substrate. *In vitro* binding of urethane to DNA did not occur in the presence of normal or activated microsomes and pH5 enzymes. The data show that the main part of the *in vivo* interaction between urethane and nucleic acids of rat liver is not attributable to metabolic utilization of ethanol or of products derived from ethanol. Further, urethane must undergo a metabolic transformation to interact with the substrate.

3101 RESPONSE OF VAGINAL EPITHELIUM AND THE QUANTITATIVE ESTIMATION OF ITS CELLULAR PROLIFERATION IN OVARIETOMIZED RATS AFTER A SINGLE ADMINISTRATION OF OESTRADIOL. (E.) Sanyal, A. K. (Inst. Med. Sci., Banaras Hindu U., Varanasi, India), S. Singh and S. P. Singh. *Acta Anat* 87(1):82-92, 1974.

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- 3144 LONG-TERM TOXICITY STUDIES OF CARMOISINE IN MICE. (E.) Mason, P. L. (British Ind. Biol. Res. Assoc., Surrey, England), I. F. Gaunt, K. R. Butterworth, J. Hardy, I. S. Kiss and P. Grasso. *Food Cosmet Toxicol* 12(5/6):601-607, 1974.
- 3145 DIMETHYL SULPHOXIDE AS A SOLVENT IN CARCINOGEN APPLICATION WITH REGARD TO THE PROLIFERATIVE ACTIVITY OF THE ADRENAL CORTEX. (E.) Amlacher, E. (Inst. Pathol., Friedrich Schiller U., Jena, Germany), M. Danz, H. Urban and K. J. Stiller. *Exp Pathol* 9(5/6):302-306, 1974.
- 3146 THE MODE OF ACTION OF CARCINOGENS WHICH CAN INDUCE TUMOURS WITH A SINGLE DOSE: A NEW HYPOTHESIS. (E.) Schoental, R. (R. Vet. Coll., London, England). *Br J Cancer* 29(1):92, 1974.
- 3147 PROPERTIES AND ENZYMIC FORMATION OF 6-OXO-BENZO(a)PYRENE RADICAL. (E.) Caspary, W. (Johns Hopkins Univ., Baltimore, Md.), S. Lesko, R. Lorentzen and P. Ts'o. *Fed Proc [II]* 33(5):1500, 1974.
- 3148 SMOKING AND LUNG CANCER. (E.) Burch, P. R. J. (Gen. Infirm., Leeds, England). *Lancet* II(7886):950, 1974.
- 3149 ACCUMULATION OF AN EPOXY INTERMEDIATE DURING THE HEPATIC MICROSOMAL METABOLISM OF *cis*-STILBENE TO *threo*-STILBENE GLYCOL DUE TO THE INHIBITION OF EPOXIDE HYDROLASE BY *trans*-STILBENIMINE. (E.) Watabe, T. (Tokyo Coll. Pharm., Japan) and K. Akamatsu. *Biochem Pharmacol* 23(13):1845-1851, 1974.
- 3150 EFFECT OF BENZO(a)PYRENE AND ITS DERIVATIVES ON THE FUNCTION OF ISOLATED RAT LIVER MITOCHONDRIA. (Rus.) Riabykh, T. P. (Inst. Exp. Clin. Oncol., Moscow, USSR) and V. A. Kobliakov. *Vopr Med Khim* 20(4):393-396, 1974.
- 3151 STUDIES IN THE INTACT MOUSE ON THE MOLECULAR EVENTS INVOLVED IN THE INITIATION OF SKIN TUMORS BY CHEMICAL CARCINOGENS AND ULTRAVIOLET IRRADIATION. (E.) Bowden, G. T. (U. Wisconsin). *Diss Abstr Int [B]* 35(5):2286, 1974.

See also:

- * (Rev): 3001, 3002, 3003, 3004, 2023, 3031
- * (Viral): 3178
- * (Immun): 3279, 3299, 3327, 3339, 3340, 3352, 3369, 3370, 3378, 3379
- * (Path): 3386
- * (Epid-Biom): 3425, 3426, 3427, 3428

3152 COMBINED EFFECT OF ROENTGEN IRRADIATION AND RADIOSTRONTIUM ON THE HAEMATOPOIETIC TISSUES AND THE DEVELOPMENT OF LYMPHOMA IN MICE. (E.) Järplid, B. (Div. Radiat. Biol., Res. Inst. Natl. Defense, Sundbyberg, Sweden). *Acta Radiol [Ther] (Stockh)* 13(3):217-231, 1974.

Female CBA mice were exposed to fractionated radiation (total dose 140, 280, or 560 r) and, in some cases, injected with ^{90}Sr (NO_3)₂ (0.1, 0.2, or 0.4 $\mu\text{C/g}$ body weight). After external whole-body irradiation, a diphasic regeneration process was observed in the thymus. When whole-body irradiation was combined with internal ^{90}Sr irradiation, no second regeneration phase occurred. Instead, the second depletion phase was accentuated and prolonged, so that the weight of the thymus did not attain normal values. Bilateral lymphocyte depletion was common and normal appearance uncommon during this second depletion phase. It is likely that after the combined treatment bilateral regeneration in the small thymic lobes and asymmetry may have the same significance for the occurrence of thymic lymphomas as unilateral thymic changes have for the occurrence of thymic lymphoma after external irradiation alone. Compared with external whole-body irradiation, combined internal and external irradiation caused delayed bone marrow regeneration, increased hematopoiesis, and produced a prolonged deficit of leukocytes in the peripheral blood. The incidence of thymic lymphoma declined with the roentgen dose when the strontium dose remained constant. Strontium injection unaccompanied by external irradiation caused no increase in the incidence of thymic lymphomas. In some cases, treatment of externally irradiated mice with ^{90}Sr caused a 2-fold increase in the incidence of thymic lymphomas. There was no significant difference in the mean latency time between thymic lymphomas and non-thymic lymphomas.

3153 LONG-TERM MORPHOLOGICAL CHANGES IN THE THYROID GLAND OF RATS EXPOSED TO TOTAL-BODY AND PERORAL RADIATION. (Rus.) Odinkova, V. A. (M. F. Vladimirovskii Sci. Res. Clin. Inst., Moscow, USSR), V. F. Kondalenko and L. A. Vasilieva. *Arkh Patol* 36(11):49-54, 1974.

Structural changes in the thyroid were studied in 43 albino random-bred male rats exposed to a total body dose of 300 r and 65 rats given ^{131}I p.o. (total dose 0.1 $\mu\text{Ci/g}$ over ten days). Combined radiation in the same dosages was given to 51 rats. Thyroid glands were examined 12 and 30 months after exposure. Peroral and combined radiation produced persistent damage to the thyroid epithelium which showed hyperplastic foci 12 months after exposure. Damaged epithelial cells contained swollen mitochondria and double cisternae in the rough endoplasmic reticulum. Some cells had many cytosomes containing lipid droplets, and the number of dense secretory granules was decreased. Whole-body irradiation produced fewer destructive changes. Thirty months after exposure, 24 of 159 irradiated animals had papillary and tubular-trabecular cancer as did four of the 100 controls. In 16 cases tumor growth was accompanied by infiltration of the thyroid stroma with lymphocytes and plasma cells.

3154 SPONTANEOUS AND RADIATION INDUCED TUMORS IN ANIMALS. (E.) Maisin, J. R. (Dept. Radiobiol., C.E.N./S.C.K., Mol, Belgium). *Biomedicine* 20(2):102-108, 1974.

Some of the physical, biological, genetic, immunological, viral, biochemical, and morphological factors related to the mechanisms of radiation induced cancers are examined. An understanding of the mechanisms of radiocarcinogenesis can not be separated from problems related to carcinogenesis in general and requires a multidisciplinary approach. Generalizations of a qualitative nature have been possible on the basis of data from animal experimentation and these may be useful in understanding how cancer can occur following irradiation in man. A quantitative determination of the risk estimate in man has not, however, been possible on the basis of the limited data available. Experiments with animals can help in the study of the mechanisms of radiocarcinogenesis, but much more experimental work is needed. Important work still to be done includes: determination of the population of cells at risk of neoplastic transformation in diverse species; determination of the mechanism by which the neoplastic transformation is induced in these cells; determination of the physical dose needed by different cells susceptible to neoplastic transformation and determination of the relative biological effectiveness; determination of the role of genetics in susceptibility to cancer induction; determination of the correlation between somatic mutations and cancers; determination of the role of radioinduced immunosuppression in cancers other than thymic lymphomas; isolation and study of viruses playing a role in the induction of tumors other than leukemia and determination of their possible activation by radiation; and determination of the effects of chemical radioprotectors and transplantation on radioinduced cancers.

3155 MALIGNANCIES FOLLOWING THERAPEUTIC AND DIAGNOSTIC IRRADIATION. A REVIEW BASED ON 6 CASES OF CHRONIC MYELOID LEUKEMIA. (Fr.) Haefliger, J. M. (Hosp. Cantonal, Geneva, Switzerland), P. Mo Costabella, P. Maurice and P. Alberto. *Praxis* 63:754-760, 1974.

Cases of chronic myeloid leukemia following therapeutic, diagnostic or occupational irradiation are reviewed, and the mechanism radiation-induced carcinogenesis is outlined. Cases of radiation-induced malignancies from the literature are surveyed. Chronic myeloid leukemia developed in five patients with pulmonary tuberculosis after small or massive doses of therapeutic or diagnostic irradiation. One case was due to occupational exposure to a total dose of 2,260 mrem over several yr. The latent period, ranging from 4 to 10 yr, was between 6 and 7 yr in most cases. The findings suggest that x-rays and radioactivity induce chronic myeloid leukemia. Studies on the mechanism of radiation-induced carcinogenesis assume specific genetic changes occur, either due to the direct action of radiation, to an indirect mechanism resulting in a primary lesion on the extra-genetic level, or to activation of a latent virus.

The susceptibility of one and the same cell varies as a function of the age of the cell and of the stage of the mitotic cycle during irradiation. Cells altered by radiation must preserve their mitotic activity to produce cancer; cancer may also be secondary to disorders in reparative processes, especially following powerful, destructive irradiation. The mitosis of altered cells can be triggered by specific or nonspecific cocarcinogens, especially in the case of cells with inherently low mitotic activity. Also, irradiation may release cocarcinogen interfering with an immune defense mechanism.

- 3156 TRAUMA AND CANCER. (E.) Tashima, C. (St. Francis Hosp., Honolulu, Hawaii). *Lancet* 7880:590-591, 1974.

A case report of a 49-yr-old Korean woman who died with carcinoma of the right breast is presented. A rather unusual sequence began with hysterectomy and oophorectomy, progressing rapidly to coronary-artery disease, and terminating in death from breast cancer within 28 months. Conjugated estrogenic hormones ("Premarin") had been administered. The author concludes that the time course of this case suggests that cancer had already been initiated in the past and that the recent events (hormonal changes, injuries, stresses, and metabolic disturbances) had enhanced the growth and spread of the cancer. It is reported that trauma may act as a co-carcinogen, though there is no evidence that single uncomplicated trauma causes cancer. Trauma does influence the site of blood-borne metastases.

- 3157 FOLLOW-UP OF DANISH THOROTRAST CASES. (E.) Faber, M. (Finsen Lab., Finsen Inst., Copenhagen, Denmark). *Proc Third Intl Meeting Toxicity Thorotrast*; 137-146, April 1974.

Thorotrast was used in Denmark between 1935 and 1947. In 1949, a follow-up study of injected patients was started. To date, 1,005 patients who were treated with thorotrast have been identified, and an additional number of cases are known who may have been injected. During the first years after thorotrast injection, 249 patients died as a result of the neurosurgical disease for which the arteriography was performed. Of the remaining thorotrast patients, 312 have since died, the death rate for males being 7.6 per year and the death rate for females being 4.0 per year. Among the mortalities, there were 28 hepatic tumors, of which 11 were typical thorotrast induced hemangio-endotheliomas with a latency period greater than 15 years. An additional 11 people died from leukemia with latency periods as low as 7-8 years. The rate of appearance of these malignancies shows no sign of decreasing.

- 3158 CARCINOMA OF THE RENAL PELVIS AFTER RETROGRADE THOROTRAST PYELOGRAPHY. (Ger.)

Jonas, D. (Med. Fac., Rheinland-Westphalian Technical Coll., Aachen, Germany) and K. H. Bigalke. *Z Urol* 66:353-357, 1973.

A case of carcinoma of the renal pelvis in a 67-yr-old patient is reported. It developed 42 yr after retrograde Thorotrast pyelography. Nodular tumors with poorly differentiated epithelial cells were found along with fibrotic degeneration of the parenchyma and deposits of Thorotrast in the right renal pelvis. The carcinoma metastasized from the right kidney to the left urethra and the bladder. The average latent time of kidney tumors resulting from Thorotrast pyelography is estimated to be 12 to 18 yr.

- 3159 THE WAVELENGTHS IN SUNLIGHT EFFECTIVE IN PRODUCING SKIN CANCER: A THEORETICAL ANALYSIS. (E.) Setlow, R. B. (Carcinogenesis Program, Oak Ridge Natl. Lab., Tenn.). *Proc Natl. Acad. Sci. USA* 71(9):3363-3366, 1974.

- 3160 HISTOCHEMICAL PHOSPHATASES AND METACHROMASIA IN MURINE TUMOURS INDUCED BY BONE SEEKING RADIONUCLIDES. (E.) Bland, M. R. (Med. Res. Council, External Staff M.R.C., Harwell, England), J. F. Loutit and J. M. Sansom. *Br J Cancer* 29(3):206-222, 1974.

- 3161 DESCRIPTION OF AN ANTIQUE RADIUM-GOBLET; A DANGEROUS CURIOSITY. (E.) De Wit, R. (Netherlands Reactor Ctr., Petten) and T. De Roo. *Med Hist* 18(3):299-303, 1974.

- 3162 CYTOGENETIC DAMAGE IN AMERICIUM POISONING. (E.) Kelly, S. (New York State Dept. Health, Albany) and A. Dagle. *NY State J Med* 74(9):1597-1598, 1974.

See also:

- * (Rev): 3005
- * (Chem): 3075, 3151
- * (Immun): 3290, 3329
- * (Epid-Biom): 3423, 3429, 3430

3163 BIOLOGICAL PROPERTIES OF A VIRUS ISOLATED FROM RADIATION-INDUCED LEUKEMIA IN C57B1 MICE. I. FIRST PASSAGES OF NATIVE VIRUS. (Fr.) Mistry, P. B. (Bergonie Fdn., Bordeaux, France) and J. F. Duplan. *Bull Cancer (Paris)* 60(3):287-300, 1973.

Cell-free extracts from the spleen, lymph nodes, and thymus of C57B1 mice with symptoms of radiation-induced leukemia were injected i.p. into young adult C57B1 mice or into the spleen or thymus of newborn or adult C57B1 mice. Within 250-350 days, lymphoid tumors developed in 100% of adult mice injected i.p. with cell-free extract: 85% had lymphoreticular tumors, and 35% of these were lymphosarcomas of the thymus. The mean survival time was 285 days. When mice were thymectomized prior to injection of the extract, 100% developed tumors of the spleen or lymph nodes after a mean latent period of 371 days. Injection of cell-free extract into the thymus induced lymphoreticular tumors into 100% of both adult and newborn mice. Thymus tumors developed in 88% of the newborns and in 60% of the adults; the mean latent periods were 419 and 367 days, resp. Injection of cell-free extract into the spleen produced lymphoreticular tumors in 67% of the newborns and 80% of the adults; the mean survival times were 394 days and 338 days, resp. Attempts to graft fragments of spleen or lymph node tumors s.c. in adult mice were unsuccessful, but 41 mice treated in this way died of leukemia. Leukemia developed in 90% of adult and 100% of newborn mice given i.p. injections of tumor cells; this leukemia involved only the spleen and lymph nodes and not the thymus. Lymphoreticular tumors developed in 40 of 45 adult C57B1 mice in which fragments from spleen or lymph node tumors were implanted under the capsule of the kidney. However, in 14 cases the implanted fragment was hypertrophied and took part in the leukemic process. By performing the same type of transplantation in F₁ hybrids of C57B1 and AKR/TLALD mice, it was demonstrated that leukemia was not caused by proliferation of the grafted cells. Lymphosarcomas of the thymus, induced by injection of extracts, were similar histologically to tumors induced by x-rays. Whenever these tumors were transplanted they produced localized or generalized lymphosarcomatosis.

3164 LYMPHOMA SUSCEPTIBILITY OF THE AKR MOUSE STRAIN ACQUIRED BEFORE THE STAGE OF IMPLANTATION. (E.) Barnes, R. D. (Clin. Res. Ctr., Harrow, England) and M. Tuffrey. *Br J Cancer* 29(5):400-402, 1974.

AKR mouse embryos at the blastocyst stage were transplanted into pseudopregnant CBA/H-T6T6 recipients. The AKR progeny were subsequently milk fed by the same recipients. The incidence of lymphomas among the ovum-transplanted AKR mice was compared with that among normally derived AKR and CBA/H-T6T6 controls. By 56 wk of age, all of the AKR controls had developed lymphomas, while most of the CBA/H-T6T6 controls lived for more than 56 wk without evidence of a tumor. All of the 53 ovum-transplanted AKR mice developed lymphomas at a time comparable with the normally derived AKR

controls, indicating that ovum transplantation and milk fostering from the CBA/H-T6T6 mice did not influence the innate tumor susceptibility of the AKR animals.

3165 A CELL SURFACE CHANGE IN MITOTIC FIBROBLASTS MONITORED WITH LECTINS. (E.) Turner, R. S. (Dept. Biochem., U. Basel, Switzerland) and M. M. Burger. *Biomed Perspect Agglutinins Invertebrate Plant Origins* 234:332-346, 1974.

Agglutinability with plant lectins is probably a host-coded property which is activated by the transformation process, regardless of whether the cells are transformed by a virus, chemical carcinogens, x-ray, or other means. Transformation by oncogenic viruses probably leads to surface changes which include increased agglutinability by lectins. That untransformed cells can be made agglutinable by brief treatment with a low concentration of any protease suggests that the lectin receptors are also present on untransformed cells. Different pairs of cells may agglutinate by different mechanisms, or a given pair of cells may show a difference in their agglutinability because there is more than one molecular alteration in their membranes. Lectin receptor sites on tumor cells may be preferentially available *in vivo* as well as *in vitro*. High agglutinability correlates with a lack of cell growth, and there are indications that there are cyclic changes in cell membranes during the cell cycle, the major portion of these changes being associated with the G-1 phase. The availability of concanavalin A receptors during the cell cycle of normal and transformed cells was studied, the results indicating that mitotic cells bind more radioactive concanavallin A than interphase cells. Similar observations were made using fluorescein-conjugated concanavallin A to visualize directly the reaction of the lectin with mitotic and interphase cells. At each mitosis, the cell may have to go through some alteration in its surface configuration which may be needed for the continuation of the cell cycle.

3166 CONCAVALIN A-INDUCED AGGLUTINATION AND TUMORIGENICITY IN VIRALLY AND SPONTANEOUSLY TRANSFORMED CELLS DERIVED FROM BALB/c MICE. (E.) Van Nest, G. A. (Coll. Med., U. Arizona, Tucson) and W. J. Grimes. *Cancer Res* 34(6):1408-1412, 1974.

The biological properties, including saturation densities, agglutination by concanavalin A, and tumorigenicity, of BALB/c fibroblasts were compared. The cell lines used include BALB/c 3T3 cells, primary BALB/c cells, and spontaneous and viral transformants of BALB/c 3T3 cells. Tumorigenicity was studied, with immunocompetent mice as hosts for tumor cells, and both tumor formation and tumor regression were determined. Agglutination by concanavalin A correlates well with the ability of a cell line to cause a tumor, but cannot predict the fate of an animal bearing a tumor, that is, tumor regression or animal death. Thus, the tumor-specific determinants detected by concanavalin A do not appear to be involved in tumor regression.

- 3167 ENHANCED Na^+ - K^+ -ACTIVATED ADENOSINE TRIPHOSPHATASE ACTIVITY IN TRANSFORMED FIBROBLASTS. (E.) Kasarov, L. B. (Albert Einstein Med. Ctr., Philadelphia, Pa.) and H. Friedman. *Cancer Res* 34(8):1862-1865, 1974.

The activity of Na^+ - K^+ -activated adenosine triphosphatase was assayed in various lines of normal and transformed mouse and rat fibroblasts maintained in tissue culture. The rapidly growing, spontaneously transformed 3T6 and 3T12 cells derived from mouse 3T3 fibroblasts, as well as 3T3 cells transformed by SV40 and murine sarcoma-murine leukemia viruses and XC cells, a line established from a Wistar rat tumor induced with Rous sarcoma, showed a 4- to 5-fold greater activity than the normal nontransformed 3T3 Swiss and 3T3 BALB/c clone A31 cell lines. Of the total adenosine triphosphatase activity, 20 to 25% represented Na^+ - K^+ -activated adenosine triphosphatase in transformed cells, but only 5% in the normal cells. A hypothesis as to the role of Na^+ - K^+ -activated adenosine triphosphatase in controlling intracellular levels of cyclic adenosine 3',5'-monophosphate in transformed cells through competition for available substrate adenosine triphosphate is discussed.

- 3168 REVERSE TRANSCRIPTASE IN PLASMA OF PATIENTS WITH BREAST CANCER. (E.) Rainer, H. (Med. U. Clin., Vienna, Austria), K. Moser and E. Deutsch. *Lancet* (7876):357-358, 1974.

The column-chromatographic enrichment of a reverse transcriptase from the plasma of a patient with breast cancer was previously reported. A similar enzyme has since been found in the plasma of two other patients with histologically verified metastatic breast cancer. The RNA-dependent DNA polymerase isolated from the three patients showed similar chromatographic and chemical behavior. The enriched enzyme preparation was fractionated and one series was preincubated with RNase, while the other was not. The DNA polymerase isolated was capable of transcribing heteropolymeric RNA fractions into an homologous DNA sequence. Thus, the enzyme isolated from the plasma of the three breast cancer patients is apparently analogous to the reverse transcriptase of oncogenic RNA viruses and the enzyme isolated from human milk. Similar RNA sequences have been found in breast carcinomas but not in benign breast tumors.

- 3169 STRUCTURAL PROTEINS OF MAMMALIAN ONCOGENIC RNA VIRUSES: MULTIPLE ANTIGENIC DETERMINANTS OF THE MAJOR INTERNAL PROTEIN AND ENVELOPE GLYCOPROTEIN. (E.) Strand, M. (Albert Einstein Coll. Med., Bronx, N.Y.) and J. T. August. *J Virol* 13(1):171-180, 1974.

The antigenic determinants of two purified protein constituents of mammalian C-type RNA viruses, the

major structural protein having a molecular weight of about 30,000 daltons and the membrane glycoproteins having molecular weights of about 70,000 daltons, were examined by competition radioimmunoassay. By the appropriate choice of antiserum and competing proteins, it was possible to distinguish type-specific, group-specific, and interspecies determinants in both the p30 major internal protein and the gp70 glycoproteins; this indicates that the antigenic properties of the viral proteins are more complex than has previously been recognized. The majority of the determinants of the major structural protein appeared to be group specific, 5-30% were interspecies determinants, and only a small fraction was type specific. In the case of the envelope glycoproteins, the chief determinants were type and group specific, only a small fraction being interspecies determinants. Some of the antigenic determinants may be a property of the carbohydrate moiety of the molecule, the structure of which is controlled by protein(s) coded for or induced by the virus.

- 3170 REVERSE TRANSCRIPTASE OF RNA TUMOR VIRUSES: IMMUNOLOGICAL RELATIONSHIPS. (E.) Todaro, G. J. (Natl. Cancer Inst., Bethesda, Md.), S. A. Aaronson, E. M. Scolnick, J. Ross and W. P. Parks. *Bibl Haematol* (39):269-271, 1973.

Studies were undertaken to determine if RNA-dependent DNA polymerase (reverse transcriptase) was specifically restricted to certain RNA tumor viruses and whether it was specifically restricted to tumor cells. All the oncogenic RNA viruses tested so far have DNA polymerase, as indicated both by the endogenous reaction with the viral RNA and by synthetic polymer-stimulated reactions with such templates as poly rA.rU, poly rI.rC and poly rA.dT. With the exceptions of visna and 'foamy' viruses, nononcogenic RNA viruses have shown no evidence of DNA polymerase activity. The polymerase seems to be a viral specific enzyme which is not found in normal cells. Despite the diversity of species of origin, host range, and biological properties of viruses with reverse transcriptase, the enzyme is uniform in its template characteristics and can be distinguished from cellular DNA polymerase. Murine virus leukemia polymerase has been partially purified and used to produce an antibody in rabbits. The antibody also inhibits the enzymatic activity of hamster, rat, and cat leukemia polymerase; it does not inhibit mouse mammary tumor virus and avian leukemia virus polymerase. An antibody prepared against the avian virus (Rous sarcoma virus) polymerase inhibits the polymerase of all major avian C-type viruses, but not any mammalian C-type virus polymerases. Thus, antibody to the reverse transcriptase will be useful not only in distinguishing C-type viruses from other retraviruses but also in identifying the species of origin of a particulate C-type virus isolate.

3171 BIOCHEMICAL AND MORPHOLOGIC EVIDENCE FOR THE PRESENCE OF AN RNA TUMOR VIRUS IN PULMONARY CARCINOMA OF SHEEP (JAAGSIEKTE). (E.) Perk, K. (Nat'l. Cancer Inst., Bethesda, Md.), R. Michalides, S. Spiegelman and J. Schlom. *J Natl Cancer Inst* 53(1):131-135, 1974.

Particles with a density of 1.15-1.20 g/ml and containing a 60-70S RNA and a reverse transcriptase were detected in purified tumor extracts and in histologically diagnosed "normal" lung tissue from Awassi sheep with adenocarcinoma in the contralateral lung. These biochemical features of RNA tumor viruses were not found in lung tissue of normal sheep or sheep with pneumonia. Typical murine type-C particles were observed by electron microscopy in tumor extracts but not in extracts of lung tissues from normal sheep. These particles averaged 100 mμ in diameter. Some possessed an outer coat, an intermediate membrane, and an electron-lucent nucleoid 50 mμ in diameter. Others possessed the electron-dense nucleoids characteristic of mature type-C particles.

3172 THE SEARCH FOR A VIRAL AGENT IN HODGKIN'S DISEASE. (E.) Hirshaut, Y. (Sloan-Kettering Inst., New York, N.Y.), R. L. Reagan, S. Perry, V. de Vita, Jr. and M. F. Barile. *Cancer* 34(4):1080-1089, 1974.

Electron microscopy and immunofluorescence techniques previously used to implicate viral agents and mycoplasma in the etiology of leukemia and Burkitt's lymphoma were employed in a search for the cause of Hodgkin's disease. In a prospective study of 26 patients, 34% had evidence of "C-type" particles in tissues or plasma pellets. No budding virus was seen. Antibody to the herpes-like virus (HLV or EBV) was as prevalent in normal controls as in patients with Hodgkin's disease and the frequency of elevated anti-HLV titers was similar. No mycoplasma was found in 41 specimens from 27 patients examined. There is no firm evidence to date linking Hodgkin's disease to the viruses known to be responsible for animal leukemias or to HLV, which is suspected to be the cause of Burkitt's lymphoma. Mycoplasma, a common contaminant in leukemia tissue, is rarely present in the malignant tissues of patients with Hodgkin's disease. Further progress depends on the identification of a richer source of virus-like particles than is offered by human plasma.

3173 ENDOGENOUS C-TYPE VIRUSES OF BALB/c CELLS: FREQUENCIES OF SPONTANEOUS AND CHEMICAL INDUCTION. (E.) Aaronson, S. A. (Nat'l. Cancer Inst., Bethesda, Md.) and C. Y. Dunn. *J Virol* 13(1):181-185, 1974.

A sensitive biological assay has been developed for studying the frequency of virus induction from mouse cells containing poorly infectious endogenous C-type viruses. The BALB/c mouse cell exerts controls over the spontaneous expression of its two endogenous viruses at distinct levels affecting virus activation and persistence. At the level of spontaneous activation,

BALB:virus-1 was much more tightly restricted than BALB:virus-2. At the level of virus persistence, however, BALB/c cells were absolutely resistant to exogenous infection by BALB:virus-2, but only relatively resistant to BALB:virus-1. The latter of the two regulatory levels appears to be the more effective in preventing spontaneous virus expression both *in vitro* and *in vivo*. The infectious center method utilized in this study for quantitating sarcoma virus-activated nonproducer cells increases the sensitivity of the assay, and is relatively unaffected by factors such as cell toxicity and variations in the kinetics of virus release.

3174 C-TYPE VIRAL PARTICLES IN A URINARY BLADDER NEOPLASM INDUCED BY *SCHISTOSOMA HAEMATOBIIUM*. (E.) Kalter, S. S. (Southwest Fdn. Res. Education, San Antonio, Tex.), R. E. Kuntz, R. L. Heberling, R. J. Helmke and G. C. Smith. *Nature* 251(5474):440, 1974.

C-type viral particles were found in one of four papillary carcinomas of capuchin (*Cebus* sp.) monkeys experimentally infected with *Schistosoma haematobium*. None were seen in two infected animals which developed only hyperplasia and squamous metaplasia, and none have been found in normal bladder tissue. Viral particles were readily observable throughout the transitional epithelial areas of the bladder carcinoma but were absent in the loose connective and smooth muscle layers. The animal in which these particles were detected showed moderate atypia and was passing the greatest number of eggs in the urine. No definite conclusions concerning the etiology of bladder cancer can be drawn from these observations.

3175 TYPE-C RNA VIRUS ISOLATED FROM SJL/J MICE. (E.) Chang, K. S. S. (Nat'l. Cancer Inst., Bethesda, Md.), L. W. Law and T. Aoki. *J Natl Cancer Inst* 52(3):777-784, 1974.

Type-C RNA viruses from spleen extracts of apparently normal SJL/J mice of various ages were isolated by tissue culture methods. The infectious virus was first detected in 20% of animals aged 1-2 months. At 4 months, 60% were positive, at 8 months, 45%, and at 12 months, 20% were positive. The infectivity titers were mostly low. The virus is designated DL-murine leukemia virus (MuLV) and was N-tropic. SJL/J mouse embryo cells were N-type in their susceptibility to murine leukemia viruses. The DL-MuLV envelope antigen was unique in that no antisera against other type-C viruses reacted with it in immunoelectron microscopy. The virus inoculated s.c. into newborn SJL/J and AL/N mice induced lymphocytic leukemia, but no acceleration or induction of development of reticulum cell neoplasm, type-B, was observed. The relative prevalence of MuLV at four to eight months of age coincides with the early phase of development of reticulum cell neoplasms commonly found in SJL/J mice. Whether this finding has any bearing on the possible etiologic role played by MuLV in the induction of neoplastic lesions in SJL/L mice remains to be elucidated.

- 3176 COEXISTENCE OF PARTICLES RESEMBLING HERPES-VIRUS AND TYPE-C VIRUS IN FEATHER FOLLICLE EPITHELIUM OF CHICKENS. (E.) Hirumi, H. (Boyce Thompson Inst., Yonkers, N.Y.), J. W. Frankel, C. O. Prickett and K. Maramorosch. *J Natl Cancer Inst* 52(1):303-306, 1974.

Three-day-old isolator derived, barrier-sustained chickens were inoculated i.p. with 0.2 ml of a mixture of avian leukosis virus (ALV; $10^{4.6}$ median tissue culture infective dose) and Marek's disease herpesvirus (MDHV; 56 focus-forming U). Six wk later feather follicles from the virus-inoculated chicks were examined by electron microscopy. Particles resembling herpesvirus and actively proliferating type-C virus, with budding forms, were detected. Since feather follicle epithelial cells from control chickens did not contain any detectable virus-like particles, it is assumed that the particles resembling herpesvirus and type-C virus in coinfecting birds were, in fact, MDHV and ALV. It is of interest that two dissimilar viruses, both associated with oncogenesis, can coexist in the same tissue.

- 3177 INTRACELLULAR FORMS OF ADENOVIRUS DNA. III. INTEGRATION OF THE DNA OF ADENOVIRUS TYPE 2 INTO HOST DNA IN PRODUCTIVELY INFECTED CELLS. (E.) Burger, H. (Inst. Genetics, U. Cologne, W. Germany) and W. Doerfler. *J Virol* 13(5):975-992, 1974.

KB cells productively infected with human adenovirus type 2 contain an alkali-stable class of viral DNA sedimenting in a broad zone between 50-90S as compared to 34S for virion DNA. This type of DNA was characterized as viral by DNA-DNA hybridization. It is extremely sensitive to shear fragmentation. Extensive control experiments demonstrated that the fast-sedimenting viral DNA is not due to an artifactual drag of virus DNA mechanically trapped in cellular DNA or to association of viral DNA with protein or RNA. Furthermore, the fast-sedimenting DNA is found after infection with multiplicities between 1-1000 plaque-forming U/cell and from 6-8 hr post-infection until very late in infection (24 hr). Analysis in dye-bouyant density gradients eliminated the possibility that the fast-sedimenting viral DNA represents supercoiled circular molecules. Upon equilibrium centrifugation in alkaline CsCl density gradients, the fast-sedimenting viral DNA banded in a density stratum intermediate between that of cellular and viral DNA. In contrast, the 34S virion DNA, isolated and treated in the same manner as the fast-sedimenting DNA, cobanded with viral marker DNA. After ultrasonic treatment of the fast-sedimenting DNA, it shifted to the density positions of viral DNA and, to a lesser extent, that of cellular DNA. The data indicate that the 50-90S viral DNA represents adenovirus DNA covalently integrated into cellular DNA.

- 3178 PREVALENCE OF ENDOGENOUS TYPE-C VIRUS IN NORMAL HAMSTER TISSUES AND HAMSTER TUMORS INDUCED BY CHEMICAL CARCINOGENS, SIMIAN VIRUS 40, AND POLYOMA VIRUS. (E.) Freeman, A. E. (Children's Hosp. Akron, Ohio), G. J. Kelloff, M. L. Vernon, W. T. Lane, W. I. Capps, S. D. Bumgarner, H. C. Turner and R. J. Huebner. *J Natl Cancer Inst* 52(5):1469-1476, 1974.

Three strains of hamsters were studied to establish the prevalence of hamster type-C viruses in normal and neoplastic tissues. Embryonic and postnatal normal tissues from LSH, NIH, and Graffi hamsters were examined for hamster type-C virus expression by complement fixation, electron microscopy, and direct isolation techniques. The only normal tissues in which hamster leukemia virus (HaLV) group-specific (gs) antigen was detected were early embryonic tissues from the Graffi hamster, and with rare exceptions, none of the embryonic or postnatal tissues contained HaLV detectable by virus isolation or electron microscopy techniques. In contrast, primary hamster tumors, induced by 3-methylcholanthrene and 7,12-dimethylbenz[a]anthracene and by simian virus 40 and polyoma virus, sometimes contained C-type particles as well as HaLV gs antigen. A high proportion of those primary tumors in which HaLV was not detected became HaLV-positive during transplant passage. It is concluded that HaLV was widespread in hamster populations, usually in a covert form, and its expression was enhanced in tumors induced by carcinogenic chemicals and DNA viruses.

- 3179 INCOMPLETE PARTICLES OF ADENOVIRUS. II. KINETICS OF FORMATION AND POLYPEPTIDE COMPOSITION OF ADENOVIRUS TYPE 2. (E.) Rosenwirth, B. (Inst. Genet., U. Cologne, W. Germany), S. Tjia, M. Westphal and W. Doerfler. *Virology* 60(2):431-437, 1974.

When KB cells growing in suspension cultures are infected with adenovirus type 2, 5-15% of the virus particles formed are incomplete in that they contain only fragments of viral DNA. The kinetics of appearance of incomplete particles and complete virions have been determined by measuring the amount of each type of particle produced at various times after infection. The incomplete particles can be detected starting 13 hr after infection. The percentage of incomplete particles is independent of the multiplicity of infection used. A comparison of the polypeptide composition of the incomplete particles with that of the complete virions by electrophoresis on polyacrylamide gel demonstrates that both types of particles contain hexons, penton base and fibers in similar relative amounts. However, the incomplete particles lack the core proteins (polypeptide V and VII) and contain a number of polypeptides which are not apparent in the complete virions or are present only in minor amounts.

3180 ULTRASTRUCTURAL FINDINGS IN MEDULLOEPITHELIOMATOUS NEOPLASMS INDUCED BY HUMAN ADENOVIRUS 12 IN RODENTS. (E.) Mukai, N. (Retina Fdn., Boston, Mass.), S. Kobayashi and M. Oguri. *Acta Neuropathol (Berl)* 28(4):293-304, 1974.

Human-adenovirus-12-induced medulloepitheliomatous tumors from seven Sprague-Dawley rats, seven Syrian hamsters, and seven C3Hf/Bi mice were examined electron microscopically. The rats and hamsters had been inoculated intracerebrally within 24 hr of birth with a single dose of 0.01 ml of human adenovirus fluid, $10^{4.1}$ TCID₅₀ HeLa cells/0.1 ml; the mice were inoculated i.p. at the same dose level. Within 2 months all of the rats and hamsters had developed solid hemispherical neoplasms in close proximity to the cerebral ventricular system. Within the same period, the mice developed multiple i.p. neoplasms. Fixation was performed by whole-body perfusion. Electron microscopic examination revealed highly primitive tumor cells containing one cilium per cell, with a 9+0 pattern within the apical region. Intracytoplasmic myelin figures were prevalent in the tumors of all three species. Intranuclear and intramitochondrial myelin figures were also common, while intramitochondrial rodlets were only occasionally observed. Types A, B, and C virions were detected in both rats and mice; no virions were detected in hamster brain tumors. Budding viruses with pedicles were fairly common in the rat and mouse tumors. Based on these data, a linear relationship between human adenovirus 12 and the malignant transformation of neuronal precursor cells is postulated.

3181 STUDIES OF NONDEFECTIVE ADENOVIRUS 2-SIMI-AN VIRUS 40 HYBRID VIRUSES. IX. TEMPLATE TOPOGRAPHY IN THE EARLY REGION OF SIMIAN VIRUS 40. (E.) Patch, C. T. (Natl. Cancer Inst., Bethesda, Md.), A. M. Lewis, Jr. and A. S. Levine. *J Virol* 13(3):677-689, 1974.

The DNAs of the five nondefective adenovirus 2 (Ad2)-simian virus 40 (SV40) hybrid viruses contain overlapping segments of the early region of wild-type SV40 DNA. The complementary DNA strands of these five viruses were separated with synthetic polyribonucleotides in isopycnic cesium chloride gradients. The relative amounts of early and late SV40 template in the DNA of each virus were determined by RNA-DNA hybridization with late lytic SV40 RNA, which contains sequences complementary to both templates. From the distribution of early and late templates in the five overlapping SV40 segments, it is concluded that either the entire early region of SV40 is symmetrically transcribed *in vivo*, or more probably, that the early SV40 templates are not contiguous, that is, that the early region of SV40 consists of at least two templates separated by late templates. This interpretation indicates that the total early region is smaller than currently believed.

3182 STUDIES ON REPAIR OF ADENOVIRUS 2 BY HUMAN FIBROBLASTS USING NORMAL, XERODERMA PIGMENTOSUM, AND XERODERMA PIGMENTOSUM HETEROZYGOUS STRAINS. (E.) Day, III, R. S. (Natl. Cancer Inst., Bethesda, Md.). *Cancer Res* 34(8):1965-1970, 1974.

Cell strains established from skin fibroblasts of 10 normal persons, 12 persons afflicted with xeroderma pigmentosum (XP), and 4 XP heterozygotes were used as hosts in studies on the repair of UV-irradiated human adenovirus 2. The virus appeared most UV light sensitive when strains belonging to XP complementation Groups A and D were used as hosts, less sensitive when strains belonging to Groups B and C were used, and least sensitive when normal or heterozygous strains were used. One-hit inactivation of adenovirus 2 required fluences of 7 to 15, 25 to 78, and 222 J/sq m, respectively, in each of these three categories of cell strains. One XP strain, judged by other methods to be capable of normal repair, was found to have a 30% repair defect by the adenovirus repair assay. This strain was derived from a biopsy taken from a patient who had severe clinical symptoms of XP and who died of metastatic melanoma.

3183 ADENOVIRUS DNA REPLICATION. I. REQUIREMENT FOR PROTEIN SYNTHESIS AND ISOLATION OF NUCLEAR MEMBRANE FRACTIONS CONTAINING NEWLY SYNTHESIZED VIRAL DNA AND PROTEINS. (E.) Yamashita, T. (St. Louis Sch. Med., Mo.) and M. Green. *J Virol* 14(3):412-420, 1974.

Nuclear membrane fractions were prepared by two procedures from KB cells pulse labeled with ³H-thymidine for 5 min late after infection with adenovirus 2: (1) the M-band technique, which yields a sharp peak containing most of the newly synthesized viral DNA, and (2) the discontinuous sucrose gradient method, which yields three membrane fractions, one of which bands at the interface between sucrose layers at density of 1.18 and 1.20 g/ml and contains most of the newly synthesized viral DNA. Studies using cyclohexamide to inhibit protein synthesis showed that proteins whose synthesis begins early after infection and occurs in the absence of viral DNA replication are required for viral DNA synthesis late after infection. To study the nature of these proteins, nuclear membrane fractions were isolated from cells labeled with ³H-leucine from 6-24 hr postinfection in the presence of arabinosyl cytosine to block viral DNA replication; the isolated fractions were analyzed by electrophoresis in sodium dodecyl sulfate polyacrylamide gels. Two proteins of molecular weights 75,000 and 45,000 were the major labeled polypeptides in the nuclear membrane fractions prepared from infected cells both by methods (1) and (2). These two proteins were not found in nuclear membrane fractions from uninfected cells. The 75,000 and 45,000 proteins may be early viral gene products that play a role in the viral DNA replication.

3184 EFFECT OF SPLENECTOMY ON THE GROWTH OF ADENOVIRUS 12 TUMORS IN HAMSTERS. (E.)

Erb, P. (Inst. Microbiol., U. Basel, Switzerland), L. Baseltgia, M. Gasser, A. Honegger and H. Loeffler. *Experientia* 30(8):943-944, 1974.

Adult Syrian hamsters of an inbred strain were subjected to splenectomy or sham splenectomy, after which they were inoculated s.c. with low or high doses of an adenovirus type 12 (Adeno 12) tumor cell line. Compared with the controls, tumor incidence was reduced and the latent period lengthened in the splenectomized animals treated with the low tumor cell dose. After inoculation of the high dose, only a small difference in tumor incidence and mean latent period was noted between the splenectomized and control animals; however, while the tumors in the controls grew progressively until death, those of the splenectomized hamsters regressed after day 5 and then started to grow again around day 12. In a second series of experiments, hamsters were inoculated with a medium dose of tumor cells; the animals were splenectomized or sham-splenectomized when the tumors became palpable. Splenectomy at the time of tumor appearance led to a regression of manifest tumors in 30% of the animals and to a significant delay in tumor growth in 70%. Bacille Calmette Guérin treatment in addition to splenectomy had no significant effect. Thus, tumor growth may be promoted by some kind of self-enhancement provided for mainly by the spleen.

3185 RETINOBLASTOMA-LIKE TUMORS INDUCED BY HUMAN ADENOVIRUS TYPE 12 IN RATS. (E.)

Kobayashi, S. (Retina Fdn., Boston, Mass.) and N. Mukai. *Cancer Res* 34(7):1646-1651, 1974.

A malignant intraocular neoplasm that resembled human retinoblastomas was produced in CD rats by injection of human adenovirus type 12. Fluid (0.01 ml) containing adenovirus type 12, $10^{7.5}$ 50% tissue culture infective doses/ml, from culture fluids of human embryo kidney cells was injected into the vitreous cavity of each newborn rat. Three of 35 virus-injected rats developed an intraocular tumor 204-288 days postinjection. Fifty additional rats were pretreated with methylnitrosourea on the 20th day of gestation; five of their offspring also developed tumors after virus injection. Tumor cells showed a marked tendency to form rosettes. A solitary cilium consisting of a typical ring of nine doublets with no axial pair (a 9 + 0 pattern) was frequently detected in the apical region of tumor cell cytoplasm. Adenovirus 12-specific T-antigen-positive particles were detectable in cells from the primary tumor tissue cultures with the immunofluorescein procedure. The limited dose of virus used, together with the presumably lower population of susceptible precursors in the retina, may account for the low incidence of tumor production in the present study.

3186 EFFECT OF IMMUNISATION WITH HEAT-KILLED MICROORGANISMS ON TRANSPLANTATION IMMUNITY TO ADENOVIRUS-12-INDUCED TUMOUR CELLS. (E.) Rees, R. C. (U. Sheffield Med. Sch., England) and C. W. Potter. *J Med Microbiol* 7(1):17-25, 1974.

Cell-free extracts of adenovirus-12-induced tumors were used to immunize CBA mice against s.c. transplantation of the homologous tumor cells. Greater immunity was obtained when heat-killed *Mycobacterium butyricum* was added to the tumor extract. Less conclusive results were obtained with *Corynebacterium parvum*. In contrast, tumor cell extract plus *Bordetella pertussis*, *Escherichia coli*, or *Staphylococcus aureus* gave significantly less immunity than did the tumor extract alone. Heat-killed *Listeria monocytogenes* and *Candida albicans* had no effect on immunity to tumor challenge. The enhancement and depression of immunity appeared to operate via cellular rather than humoral or antibody mechanisms.

3187 ETIOLOGIC STRAIN SPECIFICITIES OF THE AVIAN TUMOR VIRUSES. (E.) Beard, J. W. (Duke U. Med. Ctr., Durham, N.C.), A. J. Langlois and D. Beard. *Bibl Haematol* (39):31-44, 1973.

A revised classification of diseases induced by avian tumor viruses is presented. The classification is based on the one invariable aspect of etiologic interrelationships: specificity of influence on the myeloid and erythroid tissues. Lack of influence of some strains of avian tumor viruses on these tissues is sufficient to define a distinct group of 'sarcoma' viruses. A second and a third group are recognizable by demonstration of the etiologic individualities of myeloblastosis and erythroblastosis. The fourth group comprising myelocytomatosis agents became evidently only recently, chiefly with the demonstration of the unequivocal differences between the myeloid tissue response to BAI strain A virus and strain MC29, resp. This specificity of strain MC29 is paralleled, in part, by similarities to other strains (e.g., Furth, Loliger's strain EII) in their effects of myeloid cells and also nonhematopoietic tissues. At present, there is no evidence of a separate RNA group of lymphomatosis virus strains. Lymphomatosis is apparently an etiologically nonspecific neoplasm paralleling other conditions associated with the evident groups of leukosis strains. It is noted that classification by envelope subgroups revealed no distinction between sarcoma and leukosis viruses, or between the various leukosis strains.

3188 REVERSE TRANSCRIPTASE FROM AVIAN MYELOBLASTOSIS VIRUS: A ZINC METALLOENZYME. (E.) Auld, D. S. (Harvard Med. Sch., Boston, Mass.), H. Kawaguchi, D. M. Livingston and B. L. Vallee. *Biochem Biophys Res Commun* 57(4):967-972, 1974.

Previous evidence of a relationship between a zinc enzyme and the leukemic process led to the identifi-

cation of the RNA-dependent DNA polymerase - reverse transcriptase - of avian myeloblastosis virus as a zinc metalloenzyme. Microwave-induced emission spectrometry provides a microanalytical system capable of measuring precisely 10^{-11} to 10^{-14} g atoms of metal in microgram amounts of enzyme, orders of magnitude more sensitive than other, more conventional methods. The chromatographic fraction with the highest enzyme activity contains 1.5×10^{-11} g atoms of zinc/1.4 μ g of protein, corresponding to 1.7-1.9 g atoms of zinc/mole of enzyme for a molecular weight previously determined as 1.6 or 1.8×10^5 . The Zn/activity ratio is constant in the active fractions. Copper, iron, and manganese are absent, i.e., at or below their limits of detection (10^{-13} to 10^{-14} g atoms). Agents known to chelate zinc inhibit the enzyme while their nonchelating isomers do not. The data underline the participation of zinc in nucleic acid metabolism and bear on the lesions which accompany leukemia and zinc deficiency.

- 3189 ULTRASTRUCTURAL DISTRIBUTION OF CELL SURFACE ANTIGENS IN AVIAN TUMOR VIRUS-INFECTED CHICK EMBRYO FIBROBLASTS. (E.) Phillips, E. R. (U. Wisconsin Med. Sch., Madison) and J. F. Perdue. *J Cell Biol* 61(3):743-756, 1974.

The distribution of neoantigens in the surface membrane of avian tumor virus-infected RPL-6 chicken embryo fibroblasts was examined on carbon replicas of cell cultures using hemocyanin-labeled antibody. New determinants appearing on the cell surface of virally infected but nontransformed cells appear to be common with components of the viral envelope. These antigens exist in a diffuse, random array on the dorsal cell surface, with a denser accumulation along the cell processes. In liver cells, surface antigens are capable of several types of redistribution when activated by reaction with antibody. Leukosis virus-infected (nontransformed) cells showed two apparently independent modes of redistribution: a relocation of some antibody-related sites to the cell margin; or an involvement of essentially all sites in randomly dispersed aggregates. Viral antigenic sites on sarcoma virus-infected (transformed) cells reacted with antibody and were able to produce weak marginal relocation, but revealed a more striking tendency to migrate to some central location. The centripetal coalescence thus formed resembles the "cap" noted in other systems. Prior aggregation into "patches" may not be a prerequisite for such cap formation. Tumor-specific surface antigen detection and mapping were attempted with this technique, but the results were equivocal. An antigen possibly characteristic of rapidly dividing cells occurred in a sparse, diffuse pattern over the surface of morphologically distinct "round" cells. This antigen may be one exposed in dividing cells or perhaps specifically in dividing embryonic cells.

- 3190 ULTRASTRUCTURE OF LYMPHOID TISSUE FROM CHICKS INFECTED WITH MAREK'S DISEASE VIRUS. (E.) Frazier, J. A. (Houghton Poultry Res. Station, England). *J Natl Cancer Inst* 52(3):829-837, 1974.

Ultrastructural studies were made of thymus, bursa of Fabricius, and spleen from maternal antibody-negative (AN) chicks 3-35 days after intra-abdominal infection at one day of age with Marek's disease herpesvirus (1000 plaque-forming U). Thymus from antibody-positive (AP) birds was also examined. Initial changes in both AN and AP birds included lymphocyte destruction and regression. At 5-7 days after infection in AN birds, the tissues became infiltrated with large, pale reticulum cells, and degenerating cells and macrophages increased markedly in number. Virus particles, usually intranuclear and unenveloped, were seen mainly in reticulum cells. The particles were present from 5-9 days after infection but mainly at seven days. These changes were markedly reduced in AP birds, and virus particles were absent. From 16 to 35 days postinfection in both AN and AP birds, lymphocyte numbers increased and some tissues appeared relatively normal in structure. In both AN and AP chicks, lymphocytes with nuclear projections were rare up to 13 days post infection and fairly frequent from 16 days.

- 3191 SPECIFIC SEROLOGICAL RELATIONSHIPS AMONG PARTIALLY PURIFIED DNA POLYMERASES OF AVIAN LEUKOSIS-SARCOMA VIRUSES, RETICULOENDOTHELIOSIS VIRUSES, AND AVIAN CELLS. (E.) Mizutani, S. (McArdle Lab. Cancer Res., U. Wisconsin, Madison) and H. M. Temin. *J Virol* 13(5):1020-1029, 1974.

The partially purified DNA polymerases of reticuloendotheliosis virus (REV) and the avian leukosis-sarcoma virus group (ALV) were compared with those obtained from Muscovy duck, Pekin duck, pheasant, turkey, and rat livers. Specific serological relationships were found among the DNA polymerases of the two groups of avian viruses whose virions contain RNA and a DNA polymerase (REV and ALV) and three avian species which are natural hosts for these viruses (chicken, turkey, and Pekin duck). In addition, serological relationships were found among Trager duck spleen necrosis virus (TDSNV), chicken embryo small, and rat liver large and small DNA polymerases. No serological relationships were found with a HeLa cell DNA polymerase and an *Escherichia coli* DNA polymerase. Chicken syncytial virus (CSV) DNA polymerase showed no class-specific relationships. Some of the class-specific serological relationships were seen both by neutralization and blocking tests (between ALV and REV DNA polymerases, and between chicken large and REV DNA polymerases), while others were seen only by blocking tests. These serological relationships could result from evolutionary links and/or recombinational events. The results are consistent with the hypothesis that RNA viruses with a DNA polymerase originated from normal cellular components.

- 3192 RESPONSES OF ISOLATOR-DERIVED AND CONVENTIONAL CHICKENS TO MAREK'S DISEASE HERPESVIRUS AND AVIAN LEUKOSIS VIRUS. (E.) Frankel, J. W. (Life Sci., Inc., St. Petersburg, Fla.), W. M. Farrow, C. O. Prickett, M. E. Smith, W. F. Campbell and V. Groupe. *J Natl Cancer Inst* 52(5):1491-1497, 1974.

A flock of isolator-derived, barrier-sustained specific-pathogen-free, White Leghorn chickens (LSI-SPF) was developed to provide definitive biologic materials for the study of avian tumor viruses, particularly Marek's disease herpesvirus (MDHV) and avian leukosis virus (ALV). Unlike conventional birds, LSI-SPF chickens inoculated with MDHV (193-2660 focus-forming U, i.p.) died as early as 10 days afterward and mortality reached 100% within 12-22 days post inoculation. The time to death was related to the dose of MDHV. Typical Marek's disease (MD) symptoms and gross tumors were not seen before death. In sharp contrast, neither mortality nor tumors were observed among LSI-SPF chickens contact-exposed to birds with Marek's disease. Persistent viremia and neutralizing antibodies demonstrated that infection had occurred in LSI-SPF birds. LSI-SPF chickens kept eight wk in an ALV-monocontaminated environment had neither symptoms nor tumors, although ALV viremia was demonstrated. Mortality (81%) and tumor development (100%) occurred only in LSI-SPF chickens concurrently with exposure to both MDHV and ALV.

- 3193 RESPONSE OF TURKEYS TO INFECTION WITH VIRULENT MAREK'S DISEASE VIRUSES OF TURKEY AND CHICKEN ORIGINS. (E.) Witter, R. L. (Reg. Poultry Res. Lab., U.S. Dept. Agr., East Lansing, Mich.), J. J. Solomon and J. M. Sharma. *Am J Vet Res* 35(10):1325-1332, 1974.

Lymphoproliferative lesions were induced in 29 (15.2%) of 192 turkeys by inoculating them with strain TK809 (a virulent strain of Marek's disease (MD) virus) from a turkey and with 3 virulent MD viral strains from chickens. The lesions were observed primarily in the liver, spleen, gonads, and peripheral nerves. Some inflammatory lesions were also seen. Compared with MD viral strains of chicken origin, strain TK809 replicated better in turkey cells both *in vitro* and *in vivo* and induced a greater frequency of lesions. Although the mean infection frequency was low in surviving MD virus-inoculated turkeys as determined by serologic tests (13.9%) and viral isolation (9.6%), infection was demonstrated in 5 of 6 lesion-bearing turkeys.

- 3194 THE POSSIBLE SIGNIFICANCE OF MORPHOLOGICAL TRANSFORMATION OF HUMAN FIBROBLASTS BY EBV VIRUS *IN VITRO*. (E.) M. A. Epstein (U. Bristol Med. Sch., England) and M. Probert. *Bibl Haematol* (39):444-447, 1973.

The oncogenic potential of Epstein-Barr virus (EBV) was investigated with human fibroblasts *in vitro*.

The fibroblasts were exposed to EBV from P3HR1 Burkitt lymphoblasts and were further treated with inactivated Sendai virus to assist the entry of EBV. Such fibroblasts have undergone morphological transformation *in vitro*. The transformed cells are large and polygonal, grow in discrete, heaped-up foci, and show unusual biological characteristics. The cells have a doubling time during exponential growth of 30 hr, show a plating efficiency in 0.35% agar of about 14%, and have a low serum requirement for growth. Whether the morphological transformation corresponds to malignant transformation remains to be determined, but the high cloning efficiency in agar is a characteristic of malignant cells.

- 3195 HOST CELL REGULATION OF INDUCTION OF EPSTEIN-BARR VIRUS. (E.) Glaser, R. (Pennsylvania State U. Coll. Med., Hershey) and M. Nonoyama. *J Virol* 14(1):174-176, 1974.

Somatic-cell hybrids were prepared by fusing Raji cells with a human HeLa cell variant (D98). When the Epstein-Barr virus (EBV)-negative Raji parents were treated with iododeoxyuridine (IUDR), only the early antigen (EA) component was induced; there was no significant increase in EBV DNA and no virus particles were observed. When the D98/Raji hybrids were similarly treated, EA, virus capsid antigen (VCA), and virus particles were induced within 7 days after the removal of the IUDR. There was also a large increase in hybridizable EBV DNA. These data suggest cellular control over the degree of expression of the EBV genome.

- 3196 FELINE LEUKAEMIA VIRUS INFECTION--THE SPECTRUM OF ASSOCIATED DISEASE AND ITS RELEVANCE TO THE PATHOGENESIS AND IMMUNOLOGY OF LEUKAEMIA. (E.) Jarrett, W. F. H. (Dept. Vet. Path., U. Glasgow, Scotland), L. J. Mackey, O. Jarrett and H. M. Laird. *Bibl Haematol* (39):93-101, 1973.

A survey of naturally occurring hematopoietic neoplasms of the cat revealed that more than 80% were lymphoid neoplasms. The lymphoid neoplasia usually occurred in one of four well-defined morbid anatomical forms: multicentric, alimentary, thymic, and leukemia. Myeloproliferative neoplasms were also encountered in the cat, and may account for up to 20% of hematopoietic tumors. Inoculation of neonatal kittens with several different isolates of feline leukemia virus (FeLV) induced most of the main forms of hematopoietic neoplasia, including alimentary, thymic, and multicentric lymphosarcoma, lymphoid leukemia, myeloid leukemia, histiocytic and histiolymphocytic tumors, and one alimentary tumor containing a mixture of histiocytic and liposarcomatous elements. When kittens were infected neonatally with virus isolated from a cat with spontaneous alimentary lymphosarcoma, neoplasia developed with a linear cumulative frequency distribution of 50% in 3.5 yr. The majority of tumors in the

younger cats were alimentary lymphosarcomas, whereas lymphoblastic and myeloid leukemias occurred in cats over 1 yr of age. The major site of FeLV replication appeared to be in the bone marrow. A considerable proportion of neonatally infected kittens developed thymic atrophy and lymph node depletion; in such cases, the development of lymphoid malignancy took the form of alimentary lymphosarcoma or lymphoblastic leukemia. Cats with thymic atrophy and lymphoid depletion showed increased susceptibility to intercurrent infections. Several cases of membranous glomerulonephritis were observed in cats with lymphoid malignancy and the lesion was present in one cat with experimentally induced myeloid leukemia. It is suggested that FeLV-infected cells may travel along specific routes of the immunologic system and that cell differentiation and population expansion in that system play an important role in the genesis of the overt disease.

- 3197 PERSISTENT VIREMIA AFTER REGRESSION OF PRIMARY VIRUS-INDUCED FELINE FIBROSARCOMAS. (E.) Aldrich, C. D. (Sch. Vet. Med., U. California, Davis) and N. C. Pedersen. *Am J Vet Res* 35(11): 1383-1387, 1974.

Infectious C-type virus was isolated from the sera of cats which had rejected fibrosarcomas induced by the neonatal injection of the Snyder-Theilen strain of feline sarcoma virus (FeSV). Both transforming and nontransforming viruses were isolated from the sera of regressor cats. The serum isolates were ultrastructurally typical of C-type oncornaviruses and were antigenically cross-reactive with FeSV (FeLV). There was no correlation between tumor recurrence and the presence of transforming or nontransforming virus in the serum following primary tumor regression. The persistence of FeSV in the circulation indicated that microscopic foci of virus-producing tumor cells remained in the body after all gross tumor had disappeared or that virus replication was continuing in normal cells without exerting an oncogenic effect. In addition, the presence of infective FeSV (FeLV) in the blood of cats which had regressed primary tumors indicated that little virus-neutralizing antibody was present in the serum. However, antibody with some tumor-inhibiting effect is detectable in the sera of cats which have regressed FeSV-induced tumors.

- 3198 FELINE MALIGNANT MAMMARY TUMORS. II. IMMUNOLOGIC AND ELECTRON MICROSCOPIC INVESTIGATIONS INTO A POSSIBLE VIRAL ETIOLOGY. (E.) Weijer, K. (Netherlands Cancer Inst., Amsterdam), J. Calafat, J. H. Daams, P. C. Hageman and W. Misdorp. *J Natl Cancer Inst* 52(3):673-679, 1974.

Virus-like particles (C-type particles, those in the endoplasmic reticulum, or particles with concentric shells) were observed with the electron microscope in six or 24 feline mammary carcinomas, but not in four benign mammary tumors, four mammary glands of normal cats, or one pancreas carcinoma. They were also found in three of five pellets prepared by dif-

ferential centrifugation from mammary tumors. Of 51 mammary carcinomas tested immunologically, 11 showed fluorescence with the antifeline leukemia virus serum, but not with the antisera against mouse mammary tumor virus, Mason-Pfizer monkey virus, and the rat R-35 mammary tumor virus. The presence of feline leukemia virus (FeLV) in 21% of the mammary carcinomas of cats from households with a history of FeLV-associated disease suggested that the relationship between FeLV and feline mammary carcinomas was not coincidental. The function of the particles found in this study has not been determined but theories are presented to explain their presence.

- 3199 BREAKDOWN OF FRIEND VIRUS-INDUCED TOLERANCE AND DEVELOPMENT OF RUNTING SYNDROME IN RATS. (E.) Takeichi, N. (Hokkaido U. Sch. Med., Sapporo, Japan), H. Kaji, T. Kodama and H. Kobayashi. *Cancer Res* 34(3):543-550, 1974.

The effects of the i.p. inoculation of lymphoid cells into syngeneic inbred WKA/Mk rats made Friend virus (FV) tolerant by neonatal p.c. or i.p. injections of FV were studied. The inoculation lymphoid cells from immune donors brought about the runting syndrome (cessation of wt gain, diarrhea, ruffled hair, anemia, hunched posture, etc.) in five of seven recipients, while the inoculation of lymphoid cells from normal donors induced the runting syndrome in one of five recipients. The titer of FV in the blood decreased markedly by the inoculation of lymphoid cells, but immunological tolerance to s.c. Friend lymphoma cells was not broken in the survivors. The repeated inoculation of lymphoid cells from immune rats induced the runting syndrome in all cases. The inoculation of immune lymphoid cells into young tolerant rats induced a low incidence of the runting syndrome and a high incidence of resistance to Friend lymphoma transplants. The major pathological findings in the runted rats were atrophy of the thymus and enlargement of the spleen with a depletion of lymphocytes.

- 3200 HOST RESPONSES IN FRIEND VIRUS-INDUCED LEUKEMIA. (E.) Karnjanaprakorn-Yoosook, C. (Dept. Microbiol., Mahidol U., Bangkok, Thailand) and S. Thomson. *J Natl Cancer Inst* 53(2):407-413, 1974.

Some immunologic and nonimmunologic responses in the development and regression of Friend virus (FV)-induced leukemia were studied. FV-neutralizing antibody was detected in both A/J and (A/J X C57BL/6J)F₁ (AB6F₁) mice and their reciprocal hybrids. Subsequently, the antibody disappeared in "progressor" mice, i.e., those mice which developed leukemia and died; it persisted in "regressor" mice, i.e., those mice developing leukemia that subsequently regressed. Only regressor AB6F₁ and their reciprocal hybrids A/J mice had humoral cytotoxic activity, as detected by the chromium-release assay method. No significant interferon titer was found in regressor A/J or in regressor AB6F₁ mice and their reciprocal hybrids. Interferon is apparently not a significant factor in the control of FV-induced leukemia.

- 3201 HERPETIC INFECTION OF HUMAN EMBRYO ORGAN CULTURES. (Rus.) Malkhanov, V. V. (D. I. Ivanovskii Inst. Virolog., Moscow, USSR), R. M. Bikbulatov, O. V. Shumkin and V. M. Stackhanov. *Vopr Virusol* (6):667-670, 1973.

Herpes simplex virus (HSV) was inoculated into organ cultures of lungs and intestine from 10- to 12-wk-old human embryos. Viral titers, measured 1-7 days after inoculation of HSV, were higher in both tissues than in the culture media and reached a maximum 3-5 days after inoculation. Morphological changes were clearly evident in the lungs 48 hr after inoculation of HSV. They began at the edge and later spread to the center of these explants. Pulmonary changes resembled those previously found *in vivo* and consisted of nuclear swelling and vacuolization, chromatin margination, disappearance of nucleoli, and appearance of oxyphilic inclusions in the nuclei. Vacuoles developed in the cytoplasm and eventually caused lysis. The bronchial epithelium and connective tissue fibroblasts and poorly differentiated cells were involved. Identical morphological changes occurred in human embryonic intestine as early as 24 hr after inoculation of HSV. Changes first appeared in peripheral epithelial cells of the intestinal villi and later involved the rest of the epithelium and a few underlying fibroblasts. These findings suggest that organ cultures of lungs and intestine be used to study the pathogenesis of herpes infections.

- 3202 HERPESVIRUS SAIMIRI: VIABILITY IN FOUR SPECIES OF HEMATOPHAGOUS INSECTS AND ATTEMPTED INSECT TRANSMISSION TO MARMOSETS. (E.) Fischer, R. G. (Dept. Microbiol., U. North Dakota, Grand Forks), L. A. Falk, R. Rytter, G. J. Burton, D. H. Luecke and F. Deinhardt. *J Natl Cancer Inst* 52(5):1477-1481, 1974.

Viability of the *Herpesvirus saimiri* (HVS) genome was investigated in the stablefly *Stomoxys calcitrans*, the cat flea *Ctenocephalides felis*, and the mosquitoes *Aedes Aegypti* and *Anopheles quadrimaculatus*. The infected donors were adult white-lipped (WL) (*Saquinus fuscicollis*) and cotton-topped (CT) (*S. oedipus*) marmosets whose blood had HVS in the genome or repressed state in most lymphocytes. By the cocultivation of the dissected gut contents or ground-up whole insects on permissive vero cells, infectious virus was demonstrated immediately and at 6 hr after ingestion in all four insect species, but could not be recovered at 0.5-12 days postfeeding. Mechanical transmission from infected to non-infected CT and WL marmosets was studied by interrupted feeding procedures with *S. calcitrans*, *A. aegypti*, and the cone-nose bug *Rhodnius prolixus*. Eight recipient marmosets were kept in Horsfall-type isolation units and observed for 8-13 months. No evidence of disease or hematologic abnormalities were found, whereas two positive controls needle-inoculated with whole blood from the infected donors developed disease and died at 42 and 57 days post-inoculation.

- 3203 SPECIFICITY DIFFERENTIATION (SPD) OF ONCOGENIC AND NON-ONCOGENIC HERPESVIRUSES BY IMMUNOFLUORESCENCE. (E.) Fraser, C. E. O. (Harvard Med. Sch., Boston, Mass.) and L. V. Melendez. *J Med Prim* 3(1):73-78, 1974.

The method of specificity differentiation (SPD) as applied to indirect immunofluorescence was used to distinguish oncogenic herpesviruses from each other and from several nononcogenic herpesviruses of primates. The SPD expresses the differences between the sum of the homologous and heterologous reactions between pairs of antigens. The following viruses were compared by cross-fluorescence and were found to be clearly distinguishable from each other: *H. saimiri*, *H. ateles*, *H. simplex* type 1, *H. tamarinus*, and *H. aotus* type 2. These results confirm relationships established by reciprocal serum and cross neutralization. On the basis of SPD, even such closely related viruses and *H. simplex* types 1 and 2 could be differentiated. The data suggest that different characteristics of a virus may be defined by using biological criteria, e.g., rate of cytopathogenic effects, oncogenicity, neutralization, and immunofluorescence. SDP by immunofluorescence is a valuable additional tool in such studies, and several approaches may be necessary to adequately define closely related herpesviruses and their variants.

- 3204 COMPLEMENTATION OF ADENO-ASSOCIATED SATELLITE VIRAL ANTIGENS AND INFECTIONOUS DNA BY TEMPERATURE-SENSITIVE MUTANTS OF HERPES SIMPLEX VIRUS. (E.) Drake, S. (Baylor Coll. Med., Houston, Tex.), P. A. Schaffer, J. Esparza and H. D. Mayor. *Virology* 60(1):230-236, 1974.

The production of type 4 adeno-associated satellite virus (ASV) structural antigens and infectious DNA was studied with temperature-sensitive (ts) mutants of herpes simplex virus (HSV) types 1 and 2. The viruses were grown in confluent cultures of African green monkey kidney (Vero and BSC-1) cells. HSV-1 ts-1 was able to complement ASV with regard to antigen synthesis at both permissive and nonpermissive temperatures. Electron microscopic examination revealed no herpes or satellite virus particles in samples incubated at the nonpermissive temperatures, and all mutants yielded at least 10^{-4} -fold less virus at the nonpermissive temperature. The crude, deproteinized Hirt supernatant from ts-1-ASV-4 co-infected cultures incubated at the nonpermissive temperature contained approximately 42 $\mu\text{g/ml}$ of nucleic acids, as compared with 25 $\mu\text{g/ml}$ contained in control ASV-4 DNA. Approximately the same titers of DNA infectivity were obtained from ts 1-ASV-4 harvests at both the permissive and nonpermissive temperatures. ASV antigens were not detected in cells infected with supernatants treated with DNase prior to assay or in cells inoculated with supernatants from cells inoculated with ASV alone. Six of seven other mutants studied were unable to synthesize HSV DNA at the nonpermissive temperature. Mutants belonging to two other HSV-1 and two HSV-2 complementation groups complemented ASV antigen production at the nonpermissive temperature, while members of two other HSV-1 groups did not.

3205 ISOLATION AND CHARACTERIZATION OF A CELL LINE FROM THE COCULTIVATION OF LUCKE RENAL TUMOR CELLS AND NONTRANSFORMED FEEDER CELLS. (E.) Kucera, L. S. (Bowman Gray Sch. Med., Wake Forest U., Winston-Salem, N.C.) and J. Simonson. *J Natl Cancer Inst* 53(2):415-421, 1974.

The *in vitro* cocultivation of renal adenocarcinoma (Lucké tumor) cells with a feeder layer of frog tongue (FT) cells at 28 C yielded two newly established cell lines: LT-1 and LT-2. The LT-1 and LT-2 cells were smaller than the FT cells and were morphologically distinct from the FT cells. Also, in contrast to the FT cells, some of the LT-1 and LT-2 showed a loss of contact inhibition; in addition, they had a shorter generation time and much greater saturation densities. The LT-1 cells had a mean of 48 and a modal number of 51 chromosomes, compared with 41 and 43, resp., in the FT cells; about 69% of the LT-1 cells had a near tetraploid number of chromosomes. The LT-1 cells showed a good capacity to grow in soft agar, which the FT cells did not. Adult *Rana pipiens* inoculated with LT-1 cells, but not frogs inoculated with FT cells, developed eye chamber growths. In addition, 13 of 18 frogs inoculated with LT-1 tissue fragments developed growth in the eye chamber. Eosinophilic and Feulgen-positive intracytoplasmic inclusion bodies were detected in some LT-1 cells, electron microscopy showed that the inclusion bodies contained cell components and irregular structures of varying sizes and shapes but not intact Lucke herpesvirus (LHV) particles. Treatment of the LT-1 cells with 5-bromodeoxyuridine and 5-iododeoxyuridine did not induce LHV multiplication. The data suggest that the LT-1 and LT-2 cell lines originated from the Lucké tumor.

3206 SELECTION OF REVERTANTS OF KIRSTEN SARCOMA VIRUS TRANSFORMED NONPRODUCER BALB/3T3 CELLS. (E.) Ozanne, B. (Cold Spring Harbor Lab., N.Y.) and A. Vogel. *J Virol* 14(2):239-248, 1974.

Revertants of Kirsten sarcoma virus-transformed nonproducer BALB/3T3 cells (KA31 cells) were isolated after exposure to 5-fluorodeoxyuridine at high cell density or when suspended in methylcellulose. Revertants were also isolated by treating KA31 cells with concanavalin A, which was much more toxic for transformed cells than for normal cells. The revertants resembled BALB/3T3 cells in their morphology and growth characteristics: they had a low saturation density, failed to grow in 1% calf serum or when suspended in methylcellulose, and ceased to synthesize DNA after reaching their saturation density. Infection by murine leukemia virus rescued Kirsten sarcoma virus only from the concanavalin-A-selected variants, although all of the revertants were susceptible to infection by leukemia virus. The concanavalin A revertants also became transformed after infection with murine leukemia virus. All of the revertants could be transformed by Kirsten sarcoma virus but not by simian virus 40.

3207 ISOLATION OF LATENT HERPES VIRUS FROM HORSES. (Rus.) Yurov, K. P. (All-Union Inst. Exp. Vet. Sci.) and V. K. Sologub. *Veterinariia* (4):49-50, 1974.

Data are presented on the isolation and identification of cytopathic agents which cause spontaneous degeneration of cells in horses. Kidneys and several other organs from clinically healthy 4-7 month-old colts were trypsinized and tissue cultures were prepared. Four cytopathic agents (1P, 2P, 3P, 4P) were isolated at various passages which led to monolayer formation with small foci of rounded cells which formed clusters and separated from the glass. The isolated agents were propagated in healthy horse kidney cell cultures. The time at which the cytopathic effect appeared depended upon the inoculated dose. The sensitivity of the following cell types to these agents was tested: (1) chick embryo cells; (2) cow embryo kidney cells; (3) calf kidney cells; (4) rabbit kidney cells; (5) Syrian hamster kidney cells; (6) transplanted pig embryo kidney cell cultures; and (7) colt kidney cells. When calf kidney cultures were infected, changes occurred in the monolayer in the form of rounding of cells. Propagation was observed in a culture of rabbit kidney cells, but marked changes were not observed in several other cell cultures. Strain 2P alone caused cytopathic changes in kidney cell cultures of calf and rabbit embryo. Colt serum, from which strain 2P was isolated, labeled with fluorescein isothiocyanate, revealed that viral antigen was present in cell cultures infected with each of the isolated agents. Antiserum to rhinopneumonia virus (strain C-69) partially inhibited the propagation of strain 2P. However, since the serum was obtained from a horse in which antibodies to latent viruses may have been present, it is not possible to refer with certainty to an antigenic relationship between the newly isolated virus and the rhinopneumonia virus.

3208 DETECTION OF MASON-PFIZER VIRUS INFECTION WITH HUMAN KC CELLS CARRYING ROUS VIRUS GENOME. (E.) Ahmed, M. (Pfizer, Inc., Maywood, N. J.), W. Korol, J. Yeh, G. Schidlovsky and S. A. Mayyasi. *J Natl Cancer Inst* 53(2):383-387, 1974.

Human KC cells carrying the Rous sarcoma virus (RSV) genome formed massive syncytia when cocultivated with cells infected with the Mason-Pfizer monkey virus (M-PMV). Syncytia were also induced when a concentrated M-PMV preparation (1×10^{10} - 1×10^{11} virus particles/ml) was added directly to the KC cells. Syncytia were not observed when 118 MG cells (parent KC cells free of RSV) or XC cells were cocultivated with M-PMV-infected cells. The KC test was as sensitive as viral polymerase or immunofluorescence tests for detection of M-PMV infections. Syncytia induced by cell-free M-PMV disappeared on serial passage of the KC culture, and a chronic M-PMV infection was established. This culture then lost its capacity to form syncytia when superinfected with M-PMV or cocultivated with M-PMV-infected cells.

3209 HeLa-LIKE MARKER CHROMOSOMES AND TYPE-A VARIANT GLUCOSE-6-PHOSPHATE DEHYDROGENASE ISOENZYME IN HUMAN CELL CULTURES PRODUCING MASON-PFIZER MONKEY VIRUS-LIKE PARTICLES. (E.) Nelson-Rees, W. A. (U. California, Sch. Public Hlth., Oakland), V. M. Zhdanov, P. K. Hawthorne and R. R. Flandermeyer. *J Natl Cancer Inst* 53(3):751-757, 1974.

A virus similar to the Mason-Pfizer monkey virus (M-PMV) has been discovered in certain human cell lines, notably the AO cell line, by workers in the United States. The chromosomes and glucose-6-phosphate dehydrogenase (G6PD) mobility patterns of AO and 5 other cell lines [H.EP.#2 (clone), J96, DAPT, T-9, and CaOV] producing the same virus were studied. Conventional Giemsa staining revealed hypotriploidy for human chromosomes in all cells of all lines. Quinacrine fluorescence indicated the absence from all cells of a Y chromosome either alone or in translocation with another chromosome. A trypsin-Giemsa technique for chromosome banding revealed some marker chromosomes unique to each cell line and, several marker chromosomes common to all cell lines, as well as to several cultures of HeLa cells. G6PD mobility for all lines was of the type-A variant also characteristic of HeLa cells. While certain chromosomal differences appear to exist between cell lines studied and HeLa cell cultures, their possession in common with HeLa of an isoenzyme mobility pattern for G6PD and of unique marker chromosomes clearly establishes their derivation from the HeLa cell line.

3210 PRESENCE AND TRANSMISSION OF MAMMARY TUMOR VIRUS AND LEUKEMIA VIRUS IN THE BALB/cfRIII MOUSE. (E.) Squartini, F. (Med. Sch., U. Pisa, Italy), E. Bucciarelli and G. B. Bolis. *J Natl Cancer Inst* 53(1):137-150, 1974.

BALB/cfRIII is a high-mammary-tumor and high-leukemia strain of mice. The mammary tumor virus (MTV) and leukemia virus were demonstrated by biologic tests and electron microscopy in these mice. Experiments in which BALB/cfRIII mice were foster-nursed by C57BL mothers revealed that both MTV and leukemia virus are milk-transmitted. Tumors during the first 30 inbred generations (1292 mice) were unevenly distributed in the genealogic tree. Mammary tumors appeared more concentrated in some sublines and generations, and leukemia was more concentrated in others. The descendants of parents with mammary tumors or leukemia showed, resp., higher incidences of mammary tumors or leukemias. A strong repulsion between mammary tumors and leukemias occurred in females. In all instances, the higher the mammary tumor incidence the lower the leukemia incidence, and *vice versa*. Several of the differences found were significant. These data suggest that, although a fairly good propagation of MTV and leukemia virus was concomitant during the first 30 generations of the BALB/cfRIII strain, there were at the same time several examples of selection, segregation, and repulsion between these two viruses or their respective tumors. The data indicate some kind of interference between MTV and leukemia virus during natural life.

3211 DETECTION OF MOUSE MAMMARY TUMOR VIRUS IN CAT KIDNEY CELLS INFECTED WITH PURIFIED B PARTICLES FROM RIII MILK. (E.) Lasfargues, E. Y. (Inst. Med. Res., Camden, N.J.), B. Kramarsky, J. C. Lasfargues and D. H. Moore. *J Natl Cancer Inst* 53(6):1831-1833, 1974.

A feline kidney cell line (CRFK=F2) was experimentally infected with B particles obtained by isopycnic banding of RIII mouse milk on a Ficoll gradient. Free B particles were found in the culture supernatants 3 months postinoculation; the overall dimensions of the virions as well as the length and spacing of the spikes were the same as those of murine mammary tumor virus (MuMTV). MuMTV antigen was then detected by membrane immunofluorescence, with about 20% of the cells showing this specific antigen on their surfaces 1 yr after infection. Electron microscopy revealed formation of virions in microvilli and accumulation of specific antibodies on their surfaces. Idiogram and zymogram studies confirmed that the cultured cells were not of mouse origin. Active budding of MuMTV has not been detected in renewed attempts to infect these cells with RIII milk virus or an MuMTV from a BALB/cfC3H tumor cell line.

3212 LYMPHOCYTE INHIBITION BY MAMMARY TUMOR VIRUS IN PATIENTS WITH BREAST CANCER. (E.) Moulton, A. (Coll. Physicians Surgeons, Columbia U., New York, N.Y.), P. Lo Gerfo, N. Suciu-Foca and G. Silverstein. *J Surg Res* 16(6):592-598, 1974.

Peripheral blood lymphocytes from women with active breast cancer, benign breast disease, and nonrecurrent breast disease after mastectomy were tested for their ability to respond to the antigens of mouse mammary tumor virus (MTV) in normal and autologous serum using the mixed lymphocyte culture (MLC) and phytohemagglutinin (PHA) stimulation tests. The incidence of individuals responding to the virus by lymphocyte blastogenesis was significantly lower in the group with active breast cancer; this impairment of reactivity was proportional to the extent of the disease. This type of correlation was seen when the lymphocytes were grown with both normal and autologous serum, although the degree of stage dependency was less marked with lymphocytes grown in autologous serum. Autologous serum strongly decreased the incidence of responders among the nonrecurrence group. A significant reduction of MLC activation was seen in the presence of autologous serum as compared with pooled normal serum in the cancer patients. Sera from the active cancer patients only decreased the PHA responsiveness of autologous lymphocytes below the levels seen in normal serum. Serum alpha globulins were elevated in the patients with active disease; there was no correlation between the levels of alpha globulin and the degree of lymphocyte inhibition. The extent of tumor growth correlated positively with serum tumor-associated antigen, cytotoxic antibodies, and serum blocking factors.

- 3213 VIRUS ONCOGENESIS AND TUMOR IMMUNOGENICITY IN THE MOUSE MAMMARY TUMOR SYSTEM. (E.) Vaage, J. (Pondville Hosp., Walpole, Mass.) and D. Medina. *Cancer Res* 34(6):1319-1324, 1974.

Mammary tumorigenesis and mammary tumor transplantation immunogenicity were examined in breeding females of two syngeneic sublines of the C3H strain: in mammary tumor virus (MTV) plus nodule-inducing virus-infected C3H/Sed mice; and in MTV-free, nodule-inducing virus-infected C3Hf/Sed mice; and in explants of two separate MTV-free C3Hf/Ki hyperplastic alveolar nodule (HAN) outgrowth lines transplanted to the cleared mammary fat pads of syngeneic MTV-free C3Hf/Ki mice and transplanted to the cleared mammary fat pads of syngeneic MTV-infected C3H/Ki mice. Ninety-seven % of the C3H mice (29 of 30) developed mammary tumors at an average of 280 days. Of 43 different C3H tumors tested for transplantation immunogenicity in the C3H strain of origin, 13 (30%) had non-MTV-associated tumor-specific transplantation antigens (TSTA). All C3H tumors tested (20 of 20) for antigenicity in the C3Hf strain had MTV-associated transplantation antigens. Sixty-nine % of the C3Hf mice (34 of 49) developed mammary tumors at an average of 708 days. Of 16 different C3Hf tumors tested for antigenicity in the C3Hf strain of origin, 1 (6%) had TSTA. Tumor development in HAN line 1 was 44% at 297 days in C3Hf recipients and 100% at 175 days in C3H recipients. Tumor development in HAN line 2 was 75% at 225 days in C3Hf recipients and 87% at 142 days in C3H recipients. One of nine HAN line 1 tumors acquired TSTA during development in C3Hf/Ki mice, but none of 10 tumors acquired TSTA during development in C3H/Ki mice. One of 14 HAN line 2 tumors that arose in C3Hf/Ki mice acquired TSTA, compared with none of 15 tumors developing in C3H/Ki mice.

- 3214 SENSITIVE *IN VIVO* ASSAY FOR DETECTION OF MURINE LEUKEMIA VIRUSES. (E.) Peters, R. L. (Microbiological Assoc., Walkersville, Md.), G. J. Spahn, L. S. Rabstein, R. J. Huebner and G. J. Kelloff. *Appl Microbiol* 28(4):614-617, 1974.

A spleen antigen test (SPAT) has been developed for the *in vivo* detection of the replicative ability of murine leukemia viruses (MLV) in the BALB/c mouse strain. Virus growth in the spleen was assayed by the complement-fixation assay for MLV group-specific antigen after the injection of newborn mice. The B/c (a natural MLV isolate from a B/c tumor), Friend, Moloney, and Rauscher MLV viruses gave titers at 14 days after inoculation; these titers were generally within 1/2 log of the titer obtained at 42 days, suggesting that this assay could be used at 14 days. A positive SPAT assay, especially in conjunction with a positive CoMuL assay (an indication of good titer), was a good indicator of the inoculum's oncogenic potential. The Friend, Moloney, and Rauscher viruses, whether grown *in vitro* or *in vivo*, gave higher titers in the *in vivo* SPAT test than in a single-passage CoMuL test (*in vitro*).

- 3215 MEASUREMENT OF THE SEQUENCE COMPLEXITY OF CLONED MOLONEY MURINE LEUKEMIA VIRUS 60 TO 70S RNA: EVIDENCE OF A HAPLOID GENOME. (E.) Fan, H. (Salk Inst. Biol. Studies, San Diego, Calif.) and M. Paskind. *J Virol* 14(3):421-429, 1974.

The sequence complexity of the 60-70S RNA complex from Moloney murine leukemia virus (M-MuLV) was determined by measuring the annealing rate of radiolabeled virus-specific DNA and M-MuLV 60-70S RNA in conditions of vast RNA excess. The M-MuLV RNA annealing rate, characterized by the quantity $C_{rt1/2}$ was compared with the $C_{rt1/2}$ values for annealing of poliovirus 35S RNA (2.6×10^6 molecular wt) with poliovirus-specific DNA and Sindbis virus 42S RNA (4.3×10^6 molecular wt) with Sindbis-specific DNA. M-MuLV-specific DNA was prepared *in vitro* by the endogenous DNA polymerase reaction of M-MuLV virions, and poliovirus and Sindbis virus DNAs were prepared by incubation of viral RNA and DNA purified from avian myeloblastosis virus and an oligo deoxynucleotide primer. The poliovirus and Sindbis virus DNAs were sedimented through alkaline sucrose gradients, and those portions of the DNAs with sizes similar to the M-MuLV DNA were selected for the annealing measurements. M-MuLV was cloned on NIH-3T3 cells because of the possibility that the standard source of M-MuLV for these experiments was a mixture of viruses. The annealing measurements indicated a sequence complexity of approximately 9×10^6 daltons for the cloned M-MuLV 60-70S RNA when standardized to poliovirus and Sindbis virus RNAs. This value supports the hypothesis that each of the 35S RNA subunits of M-MuLV 60-70S RNA has a different base sequence.

- 3216 STUDIES ON INTERFERON AND MURINE LEUKEMIA SARCOMA VIRUS GROUP. (E.) Peries, J. R. (St. Louis Hosp., Paris, France), M. Canivet and M. Boiron. *Bibl Haematol* (39):331-334, 1973.

Studies on the relationship between interferon and the murine leukemia and sarcoma virus complex are reviewed. Murine RNA tumor viruses do not induce detectable levels of interferon *in vivo* or *in vitro*, but these viruses are sensitive to the antiviral action of interferon. For instance, focus formation by Moloney sarcoma virus (M-MSV) and virus yield are significantly reduced in cells pretreated with interferon preparations. When JLSV5 cells chronically infected with Rauscher murine leukemia virus (R-MLV) are treated with interferon, modified virions are formed which do not contain the same amount of RNA as the prototype C-type particles. Mouse embryo cells chronically or acutely infected with R-MLV, Moloney murine leukemia virus, or M-MSV showed a decrease in sensitivity to interferon when the latter was titrated on vesicular stomatitis virus as challenge virus. Data from several experiments suggest that the mechanism of decreased sensitivity to interferon depends on the effect of murine RNA oncogenic viruses at a level involving the final steps of the mechanism of interferon. Both Newcastle disease virus and Sendai virus multiply better in embryo cells preinfected with M-MSV.

3217 PARTICLES SIMILAR TO MOUSE LEUKAEMIA VIRUS IN EHRlich'S ASCITES CARCINOMA AND IN RETICULUM CELL NEOPLASMS TYPE B. AN ELECTRON MICROSCOPIC STUDY IN MICE. (E.) Myking, A. O. (Gade Inst., U. Bergen, Norway) and A. Abro. *Acta Pathol Microbiol Scand* [A] 82(4):571-577, 1974.

Tissue from a solid s.c. 6-day-old Ehrlich ascites carcinoma (EAC) transplant and from mesenteric lymph nodes and the spleens of two mice with reticulum cell neoplasms (RCN), histological type B, were examined electron microscopically. Virus-like particles were found in all specimens. They were seen extracellularly, within the cytoplasmic matrix, in the cytoplasmic vacuoles, and within the cisternae of the rough endoplasmic reticulum in most cells of the EAC tumor and the reticulum cell neoplasms; no particles were observed within the cell nuclei. Type A particles of 80-100 mμ in diameter were found in the EAC and RCN tumors in the cisternae, the cytoplasmic matrix, and the extracellular spaces. Type C particles of 100-140 mμ in diameter were found in the extracellular spaces and some cytoplasmic vacuoles. A particles were found budding from the cell surface and sometimes protruding into the cisternae of the endoplasmic reticulum. No type B particles characteristic of the murine mammary carcinoma were observed. In the EAC tumor, intracisternal A particles were more numerous than in the RCN tumors, while budding A particles and C particles within the cytoplasmic vacuoles and extracellular spaces were more common in the latter. The virus may be an agent causing enhanced development of RCN tumors.

3218 MOUSE LEUKEMIA VIRUS GROWTH IN MOUSE CELLS CONTAMINATED WITH *MYCOPLASMA*. (E.) McClain, K. (Div. Biol. Sci., U. Chicago, Ill.) and W. H. Kirsten. *Cancer Res* 34(2):281-285, 1974.

The growth of a mouse leukemia virus (KiMuLV) in an established mouse cell line (C3H) was examined after the line became contaminated with an unidentified *Mycoplasma* species. The contaminated cultures grew well in small plastic cultures dishes, but they could not be propagated in larger roller bottles unless the growth medium was changed frequently. Cells from *Mycoplasma*-contaminated and *Mycoplasma*-free cultures were exposed to ³H-labeled uridine for 24 hr. Culture fluids were harvested 2 or 24 hr after labeling and purified by centrifugation through discontinuous sucrose gradients. Considerably less uridine-³H-labeled virus was recovered from supernatant fluids of *Mycoplasma*-contaminated cultures than from *Mycoplasma*-free cultures. Equilibrium sedimentation in sucrose gradients of ³H-uridine material from culture supernatants of contaminated cultures produced ³H peaks at buoyant densities of 1.20 to 1.24 and 1.16 to 1.18 g/ml. Virus titers in culture fluids from *Mycoplasma*-contaminated cultures were greatly reduced as judged from viral interference tests. The viral RNA was degraded to low-molecular wt species when virions were harvested 2 to 24 hr after labeling of *Mycoplasma*-contaminated cultures.

3219 REPLICATION OF MOUSE-TROPIC AND XENOTROPIC STRAINS OF MURINE LEUKEMIA VIRUS IN HUMAN X MOUSE HYBRID CELLS. (E.) Gazdar, A. F. (Nat'l. Cancer Inst., Bethesda, Md.), E. K. Russell and J. D. Minna. *Proc Natl Acad Sci USA* 71(7):2642-2645, 1974.

NB-tropic strains of murine leukemia virus replicated efficiently in several human-mouse hybrid lines, including those that contained a complete complement of human chromosomes and many mouse chromosomes. In lines with only a few mouse chromosomes, NB-tropic viruses failed to replicate. N- and B-tropic viruses replicated in human X N-type and human X B-type cells, resp. The viral restrictive functions of the mouse Fv-1 locus were expressed in the hybrid cells, restricting the replication of N- and B-tropic strains in human X B-type and human X N-type mouse cells, resp. In contrast to mouse-tropic viruses, AT-124 virus, a xenotropic strain, replicated in human but not in mouse cells or in hybrid cells containing a complete complement of human chromosomes and near complete complement of mouse chromosomes. Hybrid lines with only a few mouse chromosomes supported AT-124 replication. These results indicate that exogenously applied mouse-tropic and xenotropic oncornaviruses exhibit different patterns of restriction in human-mouse hybrid cells.

3220 DEFICIENCY OF 60 TO 70S RNA IN MURINE LEUKEMIA VIRUS PARTICLES ASSEMBLED IN CELLS TREATED WITH ACTINOMYCIN D. (E.) Levin, J. G. (Nat'l. Inst. Child Hlth Human Develop., Bethesda, Md.), P. M. Crimley, J. M. Ramseur and I. K. Berezsky. *J Virol* 14(1):152-161, 1974.

Virus production in response to the exogenous template polyriboadenylic acid·oligo deoxythymidylic acid was monitored in AKR mouse embryo cells and JLS-V9 cells chronically infected with Rauscher leukemia virus. The production of particles with the ultrastructural appearance of C-type virions persisted for at least 6 hr in actinomycin D-treated cells infected with murine leukemia virus. This phenomenon occurred despite severe inhibition of viral RNA synthesis. Virus particles present in a 6-hr harvest sedimented in sucrose gradients with the buoyant density characteristic of RNA tumor viruses (1.16 g/cm³) and exhibited high levels of reverse transcriptase activity in response to the exogenous template in the range of untreated controls. However, RNase-sensitive endogenous activity was only 1/3 the level found in controls. This observation correlated with a marked reduction in infectivity. Kinetic studies on the appearance of labeled RNA in banded virions revealed that within the first hr after the addition of actinomycin D, the particles contained 60-70S RNA and two low-molecular wt RNA species corresponding to 8 and 4S RNA. After approximately 1 hr of incubation with actinomycin D, 60-70S RNA could not be detected and 4S RNA was the predominant species. These findings suggest that murine leukemia virus particles assembled in the presence of actinomycin D are deficient in 60-70S viral RNA.

3221 STRUCTURAL PROTEINS OF MAMMALIAN ONCOGENIC RNA VIRUSES: MURINE LEUKEMIA VIRUS NEUTRALIZATION BY ANTISERA PREPARED AGAINST PURIFIED ENVELOPE GLYCOPROTEIN. (E.) Steeves, R. A. (Albert Einstein Coll. Med., Bronx, N.Y.), M. Strand and J. T. August. *J Virol* 14(1):187-189, 1974.

Rabbit and goat antisera were prepared against the major glycoprotein constituent (gp69/71) and the p30 protein of Rauscher murine leukemia virus (MuLV). The anti-Rauscher MuLV p30 sera failed to neutralize the spleen focus-forming virus (SFFV) in Friend virus complexes, whereas the goat and rabbit anti-Rauscher MuLV gp69/71 sera were both potent. Gamma globulin, purified from the goat anti-Rauscher MuLV gp69/71 serum and diluted 10-fold to a serum-equivalent level, neutralized Friend SFFV as effectively as whole serum. Absorption of the goat anti-Rauscher MuLV gp69/71 serum with Thielens feline leukemia virus removed very little neutralizing activity, whereas absorption with Gross MuLV and Kirsten murine sarcoma virus removed some activity and absorption with Rauscher MuLV removed essentially all activity. Thus, most of the determinants involved in the neutralization of Friend SFFV by this antiserum are group-specific as well as type-specific. Rauscher SFFV was neutralized significantly more rapidly than Friend SFFV by antiserum diluted to 1/10 and 1/100.

3222 EVIDENCE FOR HELPER-INDEPENDENT MURINE SARCOMA VIRUS. II. DIFFERENCES BETWEEN THE RIBONUCLEIC ACIDS OF CLONE-PURIFIED LEUKEMIA VIRUS, HELPER-INDEPENDENT AND HELPER-DEPENDENT SARCOMA VIRUSES. (E.) Lo, A. C. H. (Cancer Res. Lab., U. Western Ontario, London, Canada) and J. K. Ball. *Virology* 59(2):545-555, 1974.

A clone of chronically infected transformed mouse cells produced a high titer (1×10^7 infectious U/ml) of helper-independent Moloney murine sarcoma virus [MuSV(R⁺T⁺)]. A second chronically infected, transformed clone produced a high titer (1×10^8 infectious U/ml) of helper-dependent MuSV [MuSV(R⁺T⁺)]. The size of the native RNA of both MuSV(R⁺T⁺) and MuSV(R⁺T⁺) was investigated in the absence of murine leukemia virus (MuLV). The results indicate that denatured RNA of MuSV(R⁺T⁺), like that of helper-independent strains of Rous sarcoma virus, contains "a" type subunits whereas denatured RNA from either Moloney MuLV or MuSV(R⁺T⁺) appears to have "b" type subunits. There was no difference in the polyacrylamide gel migration behavior of denatured RNA from Moloney MuLV and MuSV(R⁺T⁺).

3223 THE CELLULAR EVENTS ASSOCIATED WITH REGRESSION AND PROGRESSION OF MURINE (MOLONEY) SARCOMAS. (E.) Russell, S. W. (Scripps Clin. Res. Fdn., La Jolla, Calif.) and C. G. Cochrane. *Int J Cancer* 13(1):54-63, 1974.

Tumors were induced in adult and neonatal BALB/cSt mice by i.m. injections of either 10^4 or 10^6 cells from a cultured murine (Moloney) sarcoma line. Neo-

plasms that progressed were induced in neonates by either dose, and in adults only by the larger dose; adult mice receiving 10^4 cells usually developed tumors that regressed. Initially all tumors became infiltrated with polymorphonuclear leukocytes, mainly neutrophils, and edema was extensive. By the end of the second wk postinoculation, this acute inflammatory infiltrate had been replaced in adult mice by one consisting of mononuclear cells. Of significance, since mononuclear inflammatory cells were associated intimately with tumors during the process of regression, was the disappearance of these cells 12-14 days postinoculation from tumors destined to progress in adult mice. One mechanism that might contribute to loss of infiltrating mononuclear cells is inhibition by excess tumor antigen of effector cell emigration from draining regional lymph nodes.

3224 NATURALLY OCCURRING SARCOMA VIRUS OF THE BALB/cCr MOUSE. (E.) Peters, R. L. (Nat'l. Cancer Inst., Bethesda, Md.), L. S. Rabstein, R. VanVleck, C. J. Kelloff and R. J. Huebner. *J Nat'l Cancer Inst* 53(6):1725-1729, 1974.

A spontaneous chloroleukemia was observed in an 18-month-old BALB/cCr mouse. Newborn syngeneic mice inoculated with whole blood from this animal showed gross and histologic evidence of chloroleukemia by 4 wk of age. Cell-free extracts of spleen lymph nodes from these animals induced hemangiomatous and hemangiosarcomatous lesions during the first six passages. Metastases were infrequent and primarily involved the lung and regional lymph nodes. Passage of induced tumor preparations onto BALB/cCr embryo fibroblasts resulted in diffuse and focal areas of transformed cells with the morphology characteristic of murine sarcoma virus (MSV) transformation. A virus isolated from one hemangiosarcoma-derived cell line had the physical and antigenic characteristics of the type-C RNA viruses of the mouse. It produced MSV-like transformation on Fischer rat, BALB/cCr, and ACI rat cells in culture. The virus was typical of the predominant BALB/c type-C tumor isolate in that it was BALB/c tropic and of the AKR serotype.

3225 ACTIVATION OF THE MURINE SARCOMA VIRUS GENOME AFTER INFECTION WITH THE MURINE LEUKEMIA VIRUS AS DETERMINED BY CELL AGGLUTINATION. (E.) Salzberg, S. (St. Louis U. Sch. Med., Mo.) and M. Green. *J Virol* 13(5):1001-1004, 1974.

Four nonvirus-producing (NP) clonal lines derived from the same parental cell line of murine sarcoma virus (MSV)-transformed murine NIH/3T3 cells were tested for agglutination by concanavalin A (con A) before and after infection with the Moloney strain of murine leukemia virus (MLV). Prior to MLV infection, the NP clonal lines were agglutinated 12-50% by 500 µg/ml con A; this is similar to the response of normal NIH/3T3 cells. After infection with MLV, the agglutination of the NP clonal lines was greatly increased, whereas that of MLV-infected

normal NIH/3T3 cells was not. No correlation was found between the degree of agglutinability and cell growth. Sarcomagenic activity, as measured by focus formation on NIH/3T3 cells, was detected on day 2 after infection of one clonal NP line (71Ncl.6) with MLV; the degree of focus formation increased on days 3 and 4. Culture fluids from uninfected 71Ncl.6 cells and from infected and uninfected NIH/3T3 cells did not form foci on NIH/3T3 or BALB/3T3 cells. Both the 71Ncl.6 and NIH/3T3 cells released leukemia virus by 24 hr after MLV infection. The data suggest that the morphological expression of cell transformation and the surface alterations associated with increased cell agglutination are controlled by the expression of different sarcoma virus genes.

- 3226 IMMUNOLOGIC STUDY OF AN ONCORNAVIRUS ISOLATED FROM A HUMAN CANCER CELL LINE. (E.) Ilyin, K. V. (N.F. Gamaleya Inst. Epidemiol., USSR Acad. Med. Sci., Moscow), I. S. Irlin, A. F. Bykovsky, Z. Z. Spure, G. G. Miller, U. A. Abenova and V. M. Zhdanov. *Cancer* 34(3):532-538, 1974.

An oncornavirus of type B isolated from HEP2 cells was compared immunologically with other type B viruses isolated from human, monkey, and mouse tissues. Immune serum was prepared by inoculation of rabbits with HEP2 virus antigen treated with ether; the surface antigens of the virus were destroyed and the rabbits were immunized with the group-specific (internal) antigen. Tests with intracellular and extracellular HEP2 virus antigens revealed identical precipitation lines in immunodiffusion tests. The same results were obtained in comparative tests with HEP2 viral antigens and other type B viruses isolated from continuous human cell lines; no cross reaction was seen with the H22 type C virus. No cross reaction was seen between the HEP2 virus and the mouse mammary tumor virus, while rhesus monkey type B oncornavirus gave the identical precipitation line with the HEP2 test system. No detectable antigens were found in bovine serum. The test system studied apparently revealed a group-specific antigen common or related to the Mason-Pfizer group-specific antigen.

- 3227 ONCORNA-VIRAL INFORMATION IN HUMAN GLIOBLASTOMA. (E.) Birkmayer, G. D. (Dept. Cell Biol., U. Munich, W. Germany), F. Miller and F. Marguth. *J Neural Transm* 35(3):241-254, 1974.

Two of the main biochemical features characteristic for oncogenic RNA (oncornavirus) viruses were detected in human glioblastomas. In the 14 tumors tested, a RNA-instructed DNA polymerase ("reverse transcriptase") activity was present which exhibited the criteria specific for oncornavirus. It was stimutable by the synthetic polynucleotide poly-rA:oligo-dT, and was almost insensitive to actinomycin D but very sensitive to ethidiumbromide. With a simultaneous detection test, a high molecular wt RNA species was found in the subcellular fraction with the highest reverse transcriptase activity. Electron microscopy, showed that this subcellular fraction contained particles of a morphology similar to oncogenic RNA viruses of the C-type.

- 3228 ONCORNAVIRUS EXPRESSION IN HUMAN X MOUSE HYBRID CELLS SEGREGATING MOUSE CHROMOSOMES. (E.) Minna, J. D. (Natl. Heart Lung Inst., Bethesda, Md.), A. F. Gazdar, G. M. Iverson, T. H. Marshall, K. Stromberg and S. H. Wilson. *Proc Natl Acad Sci USA* 71(5):1695-1700, 1974.

Human X mouse hybrid clones obtained by fusing transformed human (VA2) cells with embryonic mouse brain cells were tested for their ability to spontaneously express type C virus particles. Previous data indicated that these hybrid cells preferentially retain human chromosome while mouse chromosomes are lost. The culture fluid from one cell line contained type-C particle markers in abundance, and typical budding C particles were observed in the cells by electron microscopy. In contrast, no particle markers were detected in the culture fluid from the parental cells and several other hybrid cell lines. Subclones of the virus-positive cell line continued to lose mouse chromosomes and varied more than 100-fold in their culture fluid DNA polymerase activity. The hybrid cell viruses, termed HMV1, banded in a sucrose gradient between 1.14 and 1.16 g/ml, possessed viral group-specific antigens, and exhibited B-tropic host range for replication in mouse embryo cells, but did not replicate in human cells when applied directly. The virus did not transform mouse cells but was able to rescue the defective murine sarcoma virus from sarcoma-positive, helper-virus-negative cells. The activity of the DNA polymerase associated with HMV1 was similar to that of Rauscher murine leukemia virus (MuLV) DNA polymerase in its preference for poly(rA) over poly(dA) as a template, use of endogenous template, detergent requirement, and inhibition by antiserum directed against MuLV-DNA polymerase. The results suggest that human X mouse hybrid cells segregating mouse chromosomes can spontaneously express endogenous type C viruses and that such hybrid cell lines may be used for the isolation of latent mammalian oncornaviruses and the analysis of gene regulation.

- 3229 THE CYTOPATHOLOGY AND DEVELOPMENT OF A HUMAN POLYOMA VIRUS (B.K.). (E.) Lecatsas, G. (Dept. Microbiol., U. Pretoria, South Africa), O. W. Prozesky and F. Scheepers. *Arch Gesamte Virusforsch* 45(4):319-327, 1974.

Fetal human fibroblasts and glial cells infected with B.K. virus were examined using light and electron microscopy. A cytopathogenic effect similar to but not identical with that caused by polyoma and simian virus 40 viruses in murine and monkey cells, resp., was observed. The first cytopathogenic effects appeared at approximately 14 days after infection, being complete by 30-40 days. Light microscopic examination of unstained monolayers revealed roughening of the cell surface, liberation of exudate, cytoplasmic vacuolization, and rounding of the cells. Stained preparations showed the same features plus a series of nuclear changes consisting of light eosinophilic patches in the nucleoplasm, chromatin clumping, and the development of a typical inclusion body. The nucleolus was not involved. Electron microscopy of

the cells revealed virus crystals in intact nuclei followed by breakdown of the nuclear membrane, clumping of the chromatin into dense masses, and liberation of the viruses, which often became associated with the cytoplasmic membrane. Liberation of virus particles from cells with intact nuclei was observed occasionally. Budding from the nucleus or cell membrane was not observed.

- 3230 POLYOMA DNA: A PHYSICAL MAP. (E.) Griffin, B. E. (Imperial Cancer Res. Fund, London, England), M. Fried and A. Cowie. *Proc Natl Acad Sci USA* 71(5):2077-2081, 1974.

The action of restriction enzymes on polyoma virus (large plaque) DNA was studied using uniformly ^{32}P -labeled viral DNA obtained from infected 3T6 or secondary mouse-embryo cells. Three restriction enzymes were used to construct a physical map of the polyoma genome. An enzyme from *Hemophilus parainfluenzae*, HpaII, cleaved the polyoma DNA into eight unique fragments (HpaII-1 to HpaII-8), ranging in size from 27.3 to 1.8% of the genome. An enzyme from *Hemophilus influenzae*, HinIII, gave two fragments comprising 56 and 44% of the genome, while an enzyme from *Escherichia coli*, EcoRI, cut at a single unique site. The physical map of the polyoma genome was constructed with methods involving further digestion of the fragments produced by EcoRI, HinIII, and HpaII, and analysis of the products of partial digestion with HpaII. Electron microscopic analysis of replicating DNA molecules (less than 50% replicated) cut with the HinIII enzyme indicated that the origin of DNA replication is 71 ± 3 map U from the EcoRI cleavage site, probably in HpaII-5. Thus, the termination of DNA replication would be about 21 map U from the EcoRI site, in HpaII-6 close to the HpaII-2-Hpa-6 junction.

- 3231 LOCATION OF THE T4 GENE 32 PROTEIN-BINDING SITE ON POLYOMA VIRUS DNA. (E.) Yaniv, M. (Pasteur Inst., Paris, France), O. Croissant and F. Cuzin. *Biochem Biophys Res Commun* 57(4):1074-1079, 1974.

E. Coli T4 gene 32 protein was bound to polyoma virus DNA and the resulting complexes examined by electron microscopy. They were seen as open circular structures with one denaturation loop/molecule. In the presence of Eco RI restriction endonuclease, the complex was cleaved once, giving rise to three classes of molecules of the same total length (equal to that of the circular complex) but with the denatured region at different distances from the near end of the molecule. Three classes of linear complexes were evident, the loop being located at 0.09 ± 0.03 , 0.22 ± 0.02 , or 0.41 ± 0.01 genome length, from the near end of the molecule. Twelve, 62, and 26% of the molecules belonged to the three classes, resp. The data suggest that in the nondefective Eco RI sensitive polyoma DNA molecule, there are three discrete regions of weak hydrogen bonding, which probably correspond to adenine-thymidine rich regions.

- 3232 THYMIDINE-MEDIATED ENHANCEMENT OF THYMIDINE KINASE INDUCTION BY POLYOMA VIRUS. (E.) Zemla, J. (Inst. Virol., Slovak Acad. Sci., Bratislava, Czechoslovakia). *Acta Virol (Praha)* 18(2):165-168, 1974.

Six-day-old confluent primary cultures of mouse embryo (ME) cells were infected with polyoma virus strain SE at a multiplicity of about 40 plaque-forming U (PFU)/cell. Cell-free extracts prepared after 0, 24, 48, and 72 hr were assayed for thymidine (dTR) kinase using ^3H -thymidine as a substrate. In some cases, dTR (100 $\mu\text{g}/\text{ml}$) or 5-fluoro-2'-deoxyuridine (FUDR) (6×10^{-5} M) was added to the cultivation medium after virus infection. Polyoma virus caused a several-fold increase in the dTR kinase activity of the ME cells, the enzymic activity reaching a peak in 24-48 hr and declining thereafter. The enzyme activity of uninfected cells was not substantially affected when dTR was present in the cultivation medium after virus inoculation; however, the activity of the infected cells was significantly enhanced. The kinetics of the enzyme induction remained unchanged. dTR was almost twice as effective as FUDR in increasing the activity of dTR kinase. The effect of FUDR could be partially reversed with dTR. These results suggest a selective stabilization of the virus-induced enzyme mediated by dTR *in vivo*.

- 3233 SURFACE MEMBRANE GLYCOPEPTIDES WHICH COINCIDE WITH VIRUS TRANSFORMATION AND TUMORIGENESIS. (E.) Glick, M. C. (Weizmann Inst. Sci., Rehovot, Israel), Z. Rabinowitz and L. Sachs. *J Virol* 13(5):967-974, 1974.

Surface glycopeptides from clones of hamster embryo cells were examined at various intervals after infections with polyoma virus (200 plaque-forming U). Two types of transformed cells were examined: clones which showed delayed transformation or an initially low tumorigenicity; and clones which were rapidly transformed, showing an initially high tumorigenicity. The glycopeptides were removed from the cell surface by trypsin and, after Pronase digestion, were examined by filtration through Sephadex G-50. With delayed transformation, a specific group of glycopeptides was increasingly evident over an 85-day period as the cells showed phenotypic properties of transformation and the ability to form tumors in young hamsters. In the other series, all but one clone of hamster embryo cells showed rapid transformation after infection with polyoma virus. This clone was less tumorigenic and showed little of the specific glycopeptides. In all cases of delayed or rapid transformation examined, the specific group of glycopeptides increased proportionately with the ability of the cells to form tumors. All of the cells derived from progressively growing tumors formed by injection of these transformed cells into adult animals showed an abundance of this group of glycopeptides. These results suggest that specific surface membrane glycopeptides accompany virus transformation and tumorigenesis. The exact chemical nature of these glycopeptides is under investigation.

- 3234 TRANSPLANTATION STUDIES ON POLYOMA VIRUS-INFECTED CULTURES OF MOUSE TOOTH GERMS. (E.) Main, J. H. P. (Fac. Dent., U. Toronto, Canada), R. J. McComb and D. Mock. *J Natl Cancer Inst* 52(3): 951-961, 1974.

Organ cultures of tooth germs infected with polyoma virus (PV) and grown *in vitro* for more than 30 days were transplanted to the s.c. tissue of the back of syngeneic mice (C3H/Bi/Mai or C3H/Bi/Lw) less than 24 hr old. Mice were divided into five series: 1) 14 mice received unmodified infected cultures; 2) 47 received cultures treated briefly with a crude polyoma antiserum; 3) 115 received cultures rinsed four times in Hanks' solution; 4) 65 received cultures treated with polyoma-hyperimmune antiserum; and 5) 38 controls received transplants of noninfected tooth germs. With four exceptions, the host mice from series 1 died early due to the effects of the virus. Transplants consisting of dysplastic, proliferating squamous epithelium were recovered from the four surviving mice in series 1 and from 32 mice in series 3. The transplants recovered from nine recipients in series 2 consisted of degenerating squamous epithelium surrounded by lymphocytes. Four recipients from series 4, 200 to 300 days old, developed fibrosarcomas at the transplantation sites. Normally structured teeth developed from transplants in 16 controls of series 5. None of the transplants developed into the expected ameloblastoma which is characteristic of neoplasia induced by PV in mice *in vivo*.

- 3235 SOME EFFECTS OF 5-BROMODEOXYURIDINE ON POLYOMA-TRANSFORMED MOUSE CELLS. (E.) Grady, L. J. (New York State Dept. Health, Albany) and A. B. North. *Exp Cell Res* 87(1):120-126, 1974.

A polyoma-transformed line of mouse cells (PY AL/N) was cultured in medium containing 5-bromodeoxyuridine (BUdR). Growth in the presence of the analog reduced, but did not eliminate, the tumorigenicity of the PY AL/N cells in 6-wk-old AL-N mice. PY AL/N cells grown for long (4 months) or short (1 wk) periods in the presence of 3, 6, or 10 $\mu\text{g/ml}$ of BUdR were agglutinated by concanavalin A (Con A) to the same extent as untreated control cells. Non-transformed AL/N cells were not agglutinated. The serum requirement for PY AL/N was also unchanged by BUdR treatment, but BUdR did reduce the number of colonies formed by PY AL/N cells suspended in soft agar; the reduction in colony formation was largely reversible after several passages in the absence of the analog. The ability of PY AL/N cells to form colonies when plated onto monolayers of AL/N cells was also reduced by BUdR treatment. Neither the growth rate nor the final saturation density of the virus-transformed cells was changed by BUdR treatment (3 $\mu\text{g/ml}$), although the saturation density was decreased by treatment with 6 or 10 $\mu\text{g/ml}$ BUdR. Nontransformed cells grown in the presence of BUdR for 2 or 3 passages were unable to divide. The BUdR-treated PY AL/N cells grew well when seeded at high densities and poorly when seeded at low densities. Base analyses indicated that BUdR substituted for 30-32% of the thymidine in virus-transformed cells grown in 3 $\mu\text{g/ml}$ of the analog.

- 3236 NATURAL LATENT INFECTION BY PAPOVAVIRUS IN THE EUROPEAN HAMSTER (*CRICETUS CRICETUS*). (Fr.) Hannoun, C. (Pasteur Inst., Paris, France), J. C. Guillon and J. Chatelain. *Ann Microbiol* 125A(2):215-226, 1974.

A new virus was isolated in 72 specimens of the wild European hamster, *Cricetus cricetus*, from Alsace. It was isolated mainly from an extract of the kidney and spleen, but also from other organs. All the strains of virus were identical. Intracerebral inoculation of the virus caused death in newborn mice around the 9th day; the only symptom was inducible attacks of tetany. Intracerebral inoculation of neonate golden hamsters retarded growth and caused loss of balance, trembling, a wet looking coat, and loss of orientation around the 8th day. Death occurred around the 11th day. Inoculation of virus elsewhere in the animal had no effect. In adult mice and hamsters the virus produced tetany, but the animals survived. In the wild hamsters there were infiltrates around the arterioles of the renal hilus or, less frequently, around the arterioles of the renal cortex, in about a third of the animals examined. In some cases there were also glomerular lesions. In experimentally infected mice and hamsters, cellular polymorphism of the meninges was observed. The virus has tentatively been classed as a papovavirus on the basis of its intranuclear localization and its size (35-40 nm).

- 3237 ON POLYOMAVIRUS INHIBITORS. II. *IN VIVO* EXPERIMENTS. (Ger.) Desselberger, U. (Inst. Virol. Seuchenhyg., Med. Hochschule Hanover, West Germany), A. Georgii, H. Ostertag, and H. Zobl. *Zbl Bakt Hyg I. Abt Orig A* 228(3):296-306, 1974.

Both inhibitor-containing, unpurified virus suspensions and inhibitor-free virus suspensions were obtained from the 8th through 12th passages of polyoma virus propagated in secondary cultures of mouse embryonic fibroblasts. The inhibitors were characterized by ability to reduce hemagglutinating activity and *in vitro* infectivity of the virus. The influence of the host cell-derived inhibitors on oncogenicity and antigenicity of the polyoma virus suspensions was investigated. Tests for infectivity *in vivo* were carried out in newborn Wistar rats taken from mothers whose serum contained no antiviral antibodies against polyoma virus. The rats were injected s.c. with the different virus preparations, and the infected animals were sacrificed after 40 days for determination of antiviral antibodies in the serum and rate of incidence of sarcomas in the kidney. The inhibitors, which had been found to be active against hemagglutination and infectivity *in vitro* proved to have no influence on antigenicity and oncogenicity *in vivo*. Dialysis, which increased the hemagglutinating activity and infectivity of the inhibitor-containing preparations *in vitro*, did not influence the oncogenicity and antigenicity significantly. Dialysis also caused no change in the hemagglutinating activity, infectivity, oncogenicity, and antigenicity of the in-

(3238-3240)

hibitor-free virus suspensions, demonstrating that neither oncogenicity nor antigenicity are influenced by differences in *in vitro* activity of the inhibitors. Masking of infectivity of inhibitor-free virus preparations with mucin did not affect oncogenicity and antigenicity significantly. Since the infectivity of unpurified polyoma virus suspensions is masked to various degrees by inhibitors from host cells, the oncogenicity and antigenicity of these suspensions cannot be characterized by the measurable infectivity *in vitro*. The findings indicate no significant correlation between either oncogenicity or antigenicity and the measured infectivity.

3238 EFFECT OF *BRUCELLA ABORTUS* INFECTION (VACCINE STRAIN 19BA) ON RAUSCHER LEUKEMIA VIRUS AND L1210 LEUKEMIA IN MICE. (E.) Veskova, T. K. (Acad. Med. Sci. USSR, Moscow), K. L. Chimishkyan and G. J. Svet-Moldavsky. *J Natl Cancer Inst* 52(5):1651-1653, 1974.

The effect of the 19BA strain of *Brucella abortus* on the lifetime of leukemic female BALB/c mice is reported. The leukemia was induced by Rauscher leukemia virus (RLV) or by transplantation of L1210 line of mouse leukemia cells. Normal mice inoculated with a single i.v. or i.p. injection of 2×10^{10} living *B. abortus* cells died in 4 days. A single injection of 2×10^3 or ten injections of 2×10^8 , however, rarely caused death. In three experiments, several groups of mice were inoculated with RLV on day 0. One group remained as the control and others, beginning the next day, were given 2×10^8 or 2×10^9 living or dead *B. abortus* i.v. or i.p. according to different schedules. All experimental animals lived significantly longer than controls. The best results were obtained in groups of animals given a single dose of 2×10^9 *B. abortus*. Dead *B. abortus*, used in only one experiment, appeared less effective in increasing the animals' lifetime. Animals given live vaccine i.p. a month before infection with RLV also showed only slight increases in lifetime. In five experiments performed with L1210 leukemia, animals were given leukemic cells i.v. and i.p., simultaneously with *B. abortus*, and again 25 days later. In all of those experiments *B. abortus* caused significant inhibition of the development of L1210 leukemia, but the degree of the effect was slight. It is concluded that the experiments indicate that leukemic mice live longer when inoculated with *B. abortus*.

3239 THE ROLE OF TUMOUR-SPECIFIC ANTIBODY AND INTERFERON PRODUCTION IN THE PATHOGENESIS OF RAUSCHER LEUKAEMIA. (E.) Toth, F. D. (U. Med. Sch., Debrecen, Hungary), L. Vaczi and M. Balogh. *Acta Virol (Praha)* 18(1):57-64, 1974.

The relationship between resistance to Rauscher virus, tumor specific antibody production, and the interferon response was studied in Balb/c, DBA/1, C57B1/10Sn, (DBA/1 X Balb/c) F_1 , and (DBA/1 X C57B1/10Sn) F_1 mice. I.p. inoculation of the virus (0.2 ml) in the Balb/c mice was followed by a rapidly pro-

gressing splenomegaly, all the animals succumbing within 40 days. The spleens of the C57B1/10Sn mice displayed only very slight enlargement, which was followed by remission starting after the second wk; none of these animals died. The spleen wt of the DBA/1 mice increased to values between those of the other two strains by the third week; this was followed by transitory, partial remission, after which the leukemia progressed again. Most of these animals died during the second exacerbation. Antibodies in the sera of the Balb/c mice never reached significant levels, those in the sera of the C57B1/10Sn mice increased rapidly and persisted at very high levels, and those in the sera of the DBA/1 mice reached lower maxima and gradually decreased after the 40th day. Rauscher virus was a weak interferon inducer in the Balb/c and C57B1/10Sn mice, but was a strong inducer in the DBA/1 animals. (DBA/1 X Balb/c) F_1 hybrids resembled the Balb/c parents in the rate of splenomegaly and the DBA/1 parents in the course of the leukemia, the tumor-specific antibody production being similar to the more resistant parental strain; interferon production resembled that in the Balb/c mice. The (DBA/1 X C57B1/10Sn) F_1 hybrids reacted similarly to the C57B1/10Sn parents, except in the interferon response, which resembled that of the DBA/1 parents. Neither the sex of the animals nor the direction of crossing affected the results. Resistance to Rauscher virus infection appears to parallel the rate of tumor-specific antibody production.

3240 HEMATOLOGICAL AND SEROLOGICAL EFFECTS OF RAUSCHER LEUKEMIA VIRUS AND EPSTEIN-BARR VIRUS ON IMMUNOSUPPRESSED NEWBORN SUBHUMAN PRIMATES. (E.) Cohen, M. H. (Natl. Cancer Inst., Bethesda, Md.), A. D. Bernstein and P. H. Levine. *Oncology* 29(5):353-363, 1974.

Hematological changes in immunosuppressed rhesus monkeys inoculated with Rauscher virus, and Rauscher-specific and Epstein-Barr virus (EBV)-specific antibodies in rhesus monkeys inoculated with these two agents are reported. Newborn immunosuppressed rhesus monkeys were inoculated s.c. and i.m. with 3 ml of ascites fluid containing 10^9 Rauscher leukemia virus cells. Two animals developed a mononucleosis-like hematologic picture with monocytosis in the peripheral blood smear and monocyte percentages five times normal values. One of the two animals received normal rabbit serum and the other received rabbit anti-monkey thymus serum. Antibody levels against EBV were measured because of the possible role of this agent in mononucleosis. Due to passive transfer of antibodies from the mothers, the titer against EBV was elevated at birth in all monkeys. However, the levels gradually fell and did not rise during or after the monocytosis associated with Rauscher virus inoculation. The Paul-Bunnell-Davidsohn heterophile test remained negative. Other immunosuppressed primates were inoculated with cells containing EBV. The EBV produced serological but not hematological changes.

- 3241 SEQUENCES PRESENT IN BOTH HUMAN LEUKEMIC CELL NUCLEAR DNA AND RAUSCHER LEUKEMIA VIRUS. (E.) Baxt, W. G. (U. California, Sch. Med. LaJolla). *Proc Natl Acad Sci USA* 71(7):2853-2857, 1974.

DNA synthesized by particulate fractions from human leukemic WBC was subfractionated by hybridization to Rauscher leukemia virus 70S RNA followed by hydroxylapatite chromatography. The Rauscher-leukemia-virus-specific DNA fraction was complementary only to sequences present in the nuclear DNA of BALB/c mouse spleens infected by this virus and the nuclear DNA from human leukemic WBC; it was not complementary to sequences present in the nuclear DNA of normal BALB/c mouse spleens or the nuclear DNA of normal human WBC. In both the murine and human leukemias, therefore, nuclear information is detectable that is specific to the oncogenic state and complementary to part of the genome of the agent known to cause the murine neoplasia.

- 3242 BURSA OF FABRICIUS AND ROUS SARCOMA TUMOR DEVELOPMENT. (E.) Smith, J. L. (Dept. Animal Sci., U. Arkansas, Fayetteville), L. T. Patterson and N. R. Gyles. *Poultry Sci* 53(5):1979, 1974.

A total of 442 chickens representing two distinct breeding groups (highly susceptible to Rous sarcomas (WL) and able to regress tumors (RR)) were subjected to surgical bursectomy at 1 day of age, subjected to bursectomy followed by cyclophosphamide injection, or left untreated. At 8 wk of age, all birds were challenged with Rous sarcoma virus. The mean antibody titers of the RR birds to *S. pullorum* (challenged at 6 wk of age) were 1:156, 1:87, and 1:31 for the control, bursectomy and bursectomy-cyclophosphamide groups, resp. The titers in the WL birds were 1:64, 1:28, and 1:2, resp. Among the birds showing a negative antibody response, progressive tumors were seen in 40% of the RR chickens and in 75% of the WL chickens. Progressive responses were seen in 7.1% (RR) and 26.1% (WL) of the positive antibody producers. Treatment with cyclophosphamide after bursectomy increased the number of progressive responses in both breeds.

- 3243 FURTHER STUDIES ON THE ABILITY OF REGRESSOR SERA TO BLOCK CELL-MEDIATED DESTRUCTION OF ROUS SARCOMA. (E.) Hayami, M. (U. Washington Med. Sch., Seattle), I. Hellstrom, K. E. Hellstrom and D. R. Lannin. *Int J Cancer* 13(1):43-53, 1974.

Six regressor sera from Japanese quails with growing sarcomas induced by the Schmidt-Ruppin strain of the Rous sarcoma virus, previously shown to be blocking when added to the mixture of target and effector (regressor spleen) cells *in vitro*, were tested for blocking effect at either the target or the effector cell level. Three sera could block only when incu-

bated with the target cells, while three other sera blocked at both the target cell and the effector cell level. Two of three regressor sera which had previously been shown to be unblocking increased cell-mediated cytotoxicity at a low dilution but had a slight blocking activity at dilution 1:128 to 1:512, which disappeared upon further dilution. The data are compatible with the hypothesis that the blocking factors operating in this system are complexes between antigens released from the tumor and antibodies formed by the host (and, occasionally, free antigen).

- 3244 SELECTIVE INCORPORATION OF HOST CELL METHIONYL-TRANSFER RNA BY RNA TUMOR VIRUSES. (E.) Wang, S. (Dept. Microbiol., Indiana U., Bloomington), R. M. Kothari, M. W. Taylor and P. P. Hung. *Biochim Biophys Acta* 340(1):52-63, 1974.

Low-molecular weight RNA isolated from Rous associated virus-1, Bryan Rous sarcoma virus grown in the presence of Rous associated virus-1, and Schmidt-Ruppin Rous sarcoma virus was compared with transfer RNA from chick embryo fibroblasts using DEAE-cellulose column chromatography. In all cases, a peak of the low-molecular weight RNA material absorbing at 260 nm eluted at the same position as the transfer RNA (about 1.2 M KCl); it formed a methylene blue-stainable band at the same position as marker transfer RNA in 10% polyacrylamide gels. A large peak eluting in the initial 0.2 M KCl wash in many cases neither accepted amino acids nor formed a band in 10% polyacrylamide gels. The patterns of amino acid acceptance of the total transfer RNA populations of three host cells (chicken liver, chick embryo fibroblasts, and Bryan Rous sarcoma virus grown in the presence of Rous associated virus-1 transformed chick embryo fibroblasts) were similar; the few possibly meaningful differences included high prolyl-tRNA acceptor activity of the fibroblastic cells. In all three strains of Rous viruses, transfer RNA for methionine was incorporated in relatively large amounts. An examination of the reversed-phase-5 chromatographic profiles of methionyl-tRNA from the viruses and host cells showed that one isoaccepting species of methionyl-tRNA was preferentially incorporated by all three viruses from the host cells. Transformylation and ribosome binding experiments indicated that this species was the internal methionyl-tRNA rather than the initiating species of methionyl-tRNA which can be formylated.

- 3245 THE PRESENCE OF UNIQUE DNA SEQUENCES AFTER VIRAL INDUCTION OF LEUKEMIA IN MICE. (E.) Sweet, R. W. (Coll. Physicians, Surgeons, Columbia U., New York), N. C. Goodman, J. R. Cho, R. M. Ruprecht, R. R. Redfield and S. Spiegelman. *Proc Natl Acad Sci USA* 71(5):1705-1709, 1974.

Previous studies have indicated that lymphocyte DNA from human leukemias and DNA from involved tissues of patients with Hodgkin's disease or Burkitt's lymphoma contain sequences which are absent from their normal counterparts. These sequences are related to those found in particulate elements asso-

ciated with these neoplasias and possessing biochemical properties characteristic of RNA tumor viruses. Similar observations have been made of unique sequences related to those of the feline virus RD-114 and found in spontaneous mastocytomas in cats. These results were extended to the classical murine model of virus-induced leukemias. Splenic DNA from BALB/c mice with leukemias induced by Rauscher leukemia virus (RLV) possessed some RLV-related sequences which do not exist in normal BALB/d DNA. Furthermore, these leukemia-specific sequences were absent from all other mouse strains examined, including AKR, a strain with a high incidence of spontaneous leukemia. The DNA of all noninfected mouse strains showed considerable homology with the RLV genome. Temperature denaturation studies indicated, however, that although the RLV-related sequences found in all normal mice were similar to each other, they were not exactly homologous with the RLV sequences. RLV-induced leukemia in BALB/c mice appears to result in the insertion of RLV sequences into cellular DNA which itself possesses only partial homology with the RLV genome.

- 3246 *IN VITRO* NEOPLASTIC TRANSFORMATION OF BOVINE EMBRYONIC UROTHELIUM BY SIMIAN VACUOLATING VIRUS 40 (SV₄₀). (E.) Elliott, A. Y. (U. Minnesota Med. Sch., Minneapolis), N. Stein and E. E. Fraley. *Invest Urol* 11(5):411-413, 1974.

The urothelium lining of a bovine embryo was minced, washed, and incubated in a medium containing 20% fetal bovine serum and 10% tryptose phosphate broth. After 7 days, when the cells had begun to form monolayer urothelial cell cultures, they were inoculated with 10⁶ particles of simian vacuolating virus 40 (SV40). After 10 days, the cultures showed evidence of transformation. The transformed bovine embryonic urothelium (T-BEU) was easily subcultured and carried through 18 passages. Monolayer subcultures were examined by electron microscopy and fluorescent antibody techniques. No virus particles were observed. Nuclear fluorescence was present in the T-BEU cells and absent in uninoculated cells, indicating the presence of SV40 T antigen in the T-BEU cells. Poorly differentiated epithelial tumors developed at the site of inoculation in 2-month-old male immunosuppressed hamsters inoculated with 4 X 10⁵ T-BEU cells. Compared with normal BEU cells, the SV40 inoculated cells showed a drastic decrease in the percentage of diploid cells.

- 3247 COMPLEMENTATION ANALYSIS OF SIMIAN VIRUS 40 MUTANTS. (E.) Chou, J. Y. (Nat'l. Inst. Arthritis, Metab., Dig. Dis., Bethesda, Md.) and R. G. Martin. *J Virology* 13(5):1101-1109, 1974.

Seventy-six new temperature-sensitive mutants of simian virus 40 (SV40) were isolated and studied by complementation analysis using a simple modification of the standard plaquing technique. The results indicated that the mutants fall into four complementation groups. The mutants of two groups (A and B) are unable to replicate viral DNA after

infection at the nonpermissive temperature, while those of the other groups are capable of viral DNA replication at the nonpermissive temperature. Of the 67 mutants analysed by complementation analyses, six belonged to complementation group A, six belonged to complementation group D, 25 belonged to complementation group B, and six belonged to complementation group C. On a statistical basis, it is highly probable that SV40 requires only four cistrons for lytic replication of the virus.

- 3248 SUPEROXIDE DISMUTASE ACTIVITY IN WI-38 CELL CULTURES: EFFECTS OF AGE, TRYPSINIZATION AND SV-40 TRANSFORMATION. (E.) Yamanaka, N. (Dept. Zool., U. of California, Davis) and D. Deamer. *Physiol Chem & Physics* 6(2):95-106, 1974.

Superoxide dismutase is investigated as a protective mechanism to determine whether peroxidative damage contributes to cellular aging. Cultured WI-38 fibroblasts, derived from human embryonic lung tissue, both normal and transformed by SV-40 virus were harvested, and the superoxide dismutase extracted. The extracts were assayed by the reduction rate of nitro blue tetrazolium, and by disc gel electrophoresis. Dismutase activity levels in cultured cells were somewhat higher than those in human embryonic lung tissue. The activity levels did not vary with cell passage levels. Electrophoresis showed bands corresponding to the cytosol and mitochondrial bands found in previous studies. In SV-40 transformed cells, the total superoxide dismutase activity was higher than normal, and the mitochondrial band was diminished or absent. Trypsinization caused decreased activity levels in both types of cells, with a 4-8-day recovery period for normal cells and one day for transformed cells. Normal cells also had a diminished mitochondrial band which reappeared with recovery of normal activity whereas transformed cells had no changes in band pattern, suggesting that mitochondrial activity is labile. Copper and zinc did not cause increase in activity levels of normal cells. It was of particular interest that the transformed cells had higher than normal levels, since they do not have the finite lifespan of normal cells.

- 3249 A NONSELECTIVE ANALYSIS OF SV40 TRANSFORMATION OF MOUSE 3T3 CELLS. (E.) Risser, R. (Cold Spring Harbor Lab., N.Y.) and R. Pollack. *Virology* 59(2):477-489, 1974.

The growth properties of 40 randomly selected colonies arising after simian virus 40 (SV40) infection of mouse 3T3 cells were investigated. Clones of cells established from these colonies were characterized as to saturation density and doubling time in 10% and 1% calf serum, growth in methyl cellulose suspension, colony formation on monolayers of normal cells, and presence of viral antigens. This analysis revealed that only 5 of the clones were indistinguishable from 3T3 cells; the remaining 35 clones differed from 3T3 cells in that they grew as rapidly in 1% calf serum as standard SV40 transformed cells.

Several patterns of transformed behavior were seen in the clones studied suggesting that the process of cellular transformation by SV40 is the result of several complicated interactions of cellular and viral genes and not simply the result of a single viral gene acting to directly transform a cell.

- 3250 THE HOST DNA SEQUENCES IN DIFFERENT POPULATIONS OF SERIALLY PASSAGED SV40. (E.) Frenkel, N. (Dept. Genetics, Weizmann Inst. Sci., Rehovot, Israel), S. Lavi and E. Winocour. *Virology* 60(1):9-20, 1974.

The closed-circular simian virus 40 (SV40) DNA which evolved during four independent sets of high-multiplicity serial passages of plaque-purified virus stocks in monkey BS-C-1 cells was studied by reassociation kinetics. The results indicate that the host DNA sequences covalently linked to viral sequences in such serially passaged SV40 DNA are predominantly of the nonreiterated type. They are similar in populations evolving during a given set of serial passages and can be different in populations arising during different sets of serial passages starting from the same plaque isolate. They do not represent a random selection of the total sequences present in the host cell genome. The data indicate that either the number of primary recombination sites on the cellular genome is very limited, or the number of such sites is large but only a few of the initial recombination products replicate preferentially.

- 3251 RELATIVE IMPORTANCE OF VIRAL AND NEOANTIGENS IN CYTOTOXIC REACTION AGAINST MURINE LEUKEMIA CELLS. (E.) Cohen, M. H. (Massachusetts Gen. Hosp., Boston), L. R. Sibal and M. A. Fink. *Immunology* 26(1):37-48, 1974.

- 3252 A COMPARATIVE STUDY OF SOME PROPERTIES OF CHROMATIN FROM NORMAL DIPLOID AND THEIR SV40 TRANSFORMED HUMAN FIBROBLASTS. (E.) Lin, J.-C. (Temple U., Philadelphia, Pa.). *Diss Abst Int B* 35(6):2569-B, 1974.

- 3253 MAPPING THE SV40 CHROMOSOME BY USE OF RESTRICTION ENZYMES. (E.) Morrow, J. F. (Stanford U., Palo Alto, Calif.). *Diss Abst Int B* 35(6):2622-B, 1974.

- 3254 STUDIES ON THE INFECTION OF ANIMAL CELLS WITH SINDBIS VIRUS: ADSORPTION, CELL SURFACE MODIFICATION, AND MATURATION. (E.) Birdwell, C. R. (California Inst. Tech., Pasadena). *Diss Abst Int B* 35(6):2605-B, 1974.

- 3255 MURINE MYELOMA NUCLEAR DNA-DEPENDENT RNA POLYMERASES: ISOLATION AND CHARACTERIZATION OF TEMPLATE INTERACTIONS. (E.) Hall, S. H. (U. Washington, St. Louis, Mo.). *Diss Abst Int B* 35(6):2612-B, 1974.

- 3256 INCREASED SUSCEPTIBILITY TO VIRUS ONCOGENESIS OF CONGENITALLY THYMUS-DEPRIVED NUDE MICE. (E.) Allison, A. C. (MRC Clin. Res. Ctr., Harrow, Middlesex, England), J. N. Monga and V. Hammond. *Nature* 252(5485):746-747, 1974.

- 3257 EFFECT OF HYPOPHYSECTOMY ON A VIRUS-INDUCED T-CELL LEUKEMIA. (E.) Bentley, H. P. (Dept. Pediatr., U. South Alabama, Mobile), E. R. Hughes and R. D. A. Peterson. *Nature* 252(5485):747-748, 1974.

- 3258 CHANGES IN THE ORAL STRUCTURES OF MICE INOCULATED WITH THE RAUSCHER LEUKEMIA VIRUS. (E.) Strobl, I. (U. Med. Sch., Debrecen, Hungary) and F. D. Toth. *J Dent Res* 53(3):770, 1974.

- 3259 *AGROBACTERIUM TUMEFACIENS* DNA AND PS8 BACTERIOPHAGE DNA NOT DETECTED IN CROWN GALL TUMORS. (E.) Chilton, M.-D. (Dept. Microbiol., U. Washington, Seattle), T. C. Currier, S. K. Farrand, A. J. Bendich, M. P. Gordon and E. W. Nester. *Proc Natl Acad Sci USA* 71(9):3672-3676, 1974.

- 3260 EVIDENCE OF HERPES GENITALIS IN MALE LINKED WITH CERVICAL DYSPLASIA IN FEMALE. (E.) Ayre, J. E. (Natl. Cancer Cytol. Ctr., Melville, N.Y.) and R. Narvaez. *Cancer Cytol* 13(2):39-41, 1973.

- 3261 APPLICATION OF AN AUTOMATED PARTICLE ANALYSIS SYSTEM TO THE QUANTITATION OF VIRUS PARTICLES. (E.) Zeve, V. H. (Frederick Cancer Res. Ctr., Fort Detrick, Md.), M. A. Gonda and J. Lebedzik. *J Natl Cancer Inst* 53(4):1099-1102, 1974.

- 3262 TRANSCRIPTION OF THE GLOBIN GENE IN AVIAN ERYTHROBLASTOSIS VIRUS-TRANSFORMED CELLS NOT PRODUCING HEMOGLOBIN. (E.) Therwath, A. (ISREC, Dept. Biol. Molec., Lausanne, France) and K. Scherrer. *Experientia* 30(6):710, 1974.

- 3263 STUDIES ON FELINE LYMPHOSARCOMA IN THE SYDNEY AREA. (E.) Sabine, M. (Dept. Vet. Pathol., U. Sydney, Australia), R. G. Wright and D. N. Love. *Aust J Exp Biol Med Sci* 52 (Pt. 2):331-340, 1974.

- 3264 THE ULTRASTRUCTURE AND VIRUS-LIKE PARTICLES IN FELINE MAMMARY CARCINOMAS. (E.) Von Bomhard, D. (Fac. Vet. Med., U. Munich, Germany) and S. G. De S. Wettimuny. *J Comp Pathol* 84:429-436, 1974.

- 3265 VIRAL INFECTION AND HOST DEFENSE. (E.) Carter, W. A. (Roswell Park Mem. Inst., Buffalo, N.Y.) and E. De Clercq. *Science* 186(4170):1172-1178, 1974.

3266 TRANSMISSIBLE DISEASE AND BLOOD TRANSFUSION. (E.) Dodd, R. Y. (Blood Res. Lab., American Natl. Red Cross, Bethesda, Md.). *Science* 186(4169):1138-1139, 1974.

3267 AN IMMUNOELECTRON MICROSCOPY STUDY OF SOEHNER-DMOCHOWSKI MURINE SARCOMA VIRUS FOLLOWING PASSAGE IN RATS AND HAMSTERS. (E.) Hiraki, S. (U. Texas System Cancer Ctr., Houston), J. C. Chan, R. L. Hales and L. Dmochowski. *Cancer Res* 34(11):2906-2910, 1974.

3268 HERPESVIRUSES AND ONCOGENESIS. (E.) Klein, G. (No affiliation). *Nature* 252 (5482):348-350, 1974.

3269 BACTERIAL MUTATION AFFECTING T4 PHAGE DNA SYNTHESIS AND TAIL PRODUCTION. (E.) Simon, L. D. (Fox Chase Ctr. Cancer Med. Sci., Philadelphia, Pa.), D. Snover and A. H. Doermann. *Nature* 252(5483):451-455, 1974.

3270 A STABLE SYNCYTIAL MUTANT OF HERPES SIMPLEX TYPE 2 VIRUS. (E.) Anonymous. *J Gen Virol* 23(2):219-224, 1974.

3271 INHIBITION OF SIMIAN VIRUS 40 DNA SYNTHESIS BY FROG VIRUS 3. (E.) Anonymous. *J Gen Virol* 23(3):335-339, 1974.

See also:

- * (Rev): 3001, 3006, 3007, 3008, 3009, 3016, 3018, 3020
- * (Chem): 3062, 3063
- * (Immun): 3281, 3283, 3284, 3290, 3296, 3320, 3326, 3330, 3339, 3344, 3345, 3350, 3357, 3362, 3364, 3377

- 3272 SERUM ANTIBODY IN PATIENTS WITH MAMMARY DISEASE. (E.) Humphrey, L. J. (Dept. Surg., U. Kansas Med. Ctr., Kansas City), N. C. Estes, P. A. Morse, Jr., W. R. Jewell, R. A. Boudet and M. J. K. Hudson. *Cancer* 34(4):1516-1520, 1974.

Antibody to a breast cancer antigen was detected by immunodiffusion or complement fixation in at least one serum sample in 46% of 84 patients with a diagnosis of carcinoma, 34% of 96 patients with fibrocystic disease, and 25% of 44 patients with fibroadenoma. A single serum sample obtained from screenees of the Detection Center for Breast Diseases in Kansas was tested by immunodiffusion only, and antibody was found in 3 of 206 screenees (1.5%). Eleven of 13 patients with breast cancer metastatic to lymph nodes and no detectable serum antibody either had recurrence or were dead within 12 months of mastectomy. Fifteen of 18 patients with breast cancer metastatic to lymph nodes and with detectable serum antibody were alive and free of disease for up to 24 months. The presence of serum antibody and histology of tumors were not in any way correlated. Data to date indicate that serum antibody in the patient with breast disease cannot be used at this time as an "early detection test." As a seroprognostic factor in patients with breast cancer metastatic to lymph nodes, the finding of antibody has great promise.

- 3273 CELLULAR SITES OF IMMUNOGLOBULINS. IV. STUDIES OF ANTRAL MUCOSA OF HUMAN STOMACHS. (E.) Chen, S.-T. (Second Surg. Dept., Fac. Med., Kyoto U., Japan) and T. Tobe. *Digestion* 10(3):177-183, 1974.

Fluorescent antibody techniques were used to study the distribution of immunoglobulin (Ig)-containing cells in the gastric antral mucosa of five patients with chronic gastritis, seven patients with benign gastric ulcer, three patients with adenocarcinomas, two patients with undifferentiated cell carcinomas, and one patient with a lymphosarcoma. IgA-containing cells predominated in every specimen, accounting for 58-94% (mean 76.2%) of the fluorescent cells in single-stained preparations; these cells were diffusely distributed throughout the interstitial spaces between the crypts and in the lamina propria. IgM-containing cells accounted for 3-27% (13.4%) of the fluorescent cells and tended to be concentrated in the interstitium of the glands. IgG-containing cells, 3-28% (10.4%), were usually found at the base of the lamina propria near the capillaries. In the cancer patients, IgG-containing immunocytes were often visible in intermuscular spaces near the site of tumor cell invasion beneath the cancers. Some malignant cells from one patient with undifferentiated cell carcinoma and from the patient with lymphosarcoma appeared to be stained with anti-IgG and, to a lesser extent, with anti-IgM fluorescence. The finding of IgG bound to cells of gastric malignancy may be evidence of immune responses to the tumor.

- 3274 DISTRIBUTION OF CYTOTOXIC ANTIBODIES AND ANTIBODIES BLOCKING THE CYTOTOXIC REACTION IN CLASSES OF IMMUNOGLOBULINS IN CHILDREN WITH ACUTE LEUKEMIA. (Rus.) Stefani, D. B. (Inst. Pediatr. Child Surg. Moscow, USSR) and V. V. Smirnov. *Pediatrics* (8):12-15, 1974.

Studies were conducted on immunoglobulin-related cytotoxic antibodies and antibodies blocking the cytotoxic reaction in children with acute leukemia. Sera were studied from five patients with acute leukemia, seven patients in remission, and 12 patients immunized by allogenic leukemic cells during complete remission (27 injections). No cytotoxic sera were found in unimmunized patients. The sera of five of the 12 immunized children revealed cytotoxic antibodies in titers from 1:8 to 1:16. In four patients the antibodies in the cytotoxic sera were associated with IgG and in one patient with IgM (the IgM level in the patient's serum was twice as high as the average for the age group; the IgG and IgA levels were 1840 and 210 mg%, resp.). The blocking effect of the sera was found to be associated with IgA.

- 3275 CELL LOCALIZATION OF ALPHA-FETOPROTEIN IN LIVER DISEASE. (Fr.) Uriel, J. (Cancer Res. Inst., Villejuif, France). *Bull. Cancer (Paris)* 60(4):363-370, 1973.

The intracellular site of α -fetoprotein synthesis was studied in fetal and newborn rats and in rat and human hepatocellular carcinomas by cell affinity labeling with ^3H -estrone and ^3H -estradiol. In livers from fetal and newborn rats, the radiolabeled cells were of the hepatocyte type, and no radioactivity was detected in hematopoietic cells, bile duct cells, and Kupffer's cells. The radiolabeled cells were either isolated or clustered in small groups which were irregularly distributed, but were located primarily in the vicinity of large blood vessels (fetal liver) and in portal areas (newborns and tumoral livers). The total number of labeled cells relative to the whole liver cell population was variable but consistently low, amounting to 1 to 2%. The labeled cells were round or oval in shape, and relatively small (between 8 and 12 μ). Morphologically, they were intermediate between small hepatocytes and cells lining the bile ducts. In hepatocellular carcinomas, no radioactivity was found in hypertrophic and hyperplastic tumor hepatocytes, in Kupffer's cells, cuboidal cells lining the bile ducts, nor in nontumorous hepatocytes. Labeling occurred most often in the cytoplasm and sometimes in the nuclei or cell membrane. The labeled cells, round or oval in shape, and apparently intermediate between small hepatocytes and bile duct cells, were localized most often isolated among tumorous hepatic cords, grouped in portal areas in zones of neocanalicular regeneration, or included in stromal reaction zones. A relatively small number of α -fetoprotein producing cells was found sufficient to maintain a high serum concentration. The intermediary α -fetoprotein cells may contribute to hepatic regeneration following liver injury of either neoplastic or nonneoplastic origin.

- 3276 α_1 -FOETOPROTEIN IN MALIGNANT TUMORS. (Ger.)
Lehmann, F. G. (Med. U. Marburg, Germany)
and D. Lehmann. *Klin Wochenschr* 52(5):222-232, 1974.

α_1 -Fetoprotein (AFP) was extracted from eight primary liver cell carcinomas and three other carcinomas with AFP synthesis. Quantitative measurements in human tissues and in biological fluids gave the following results: 1) the AFP concentration in human tissue varied between 12 $\mu\text{g/g}$ and 630 $\mu\text{g/g}$ wet wt. When the histological aspect was similar, the AFP level in primary tumor tissue and in metastases was in the same range. 2) Total AFP content ranged from 0.8 mg to 1415 mg/tumor. 3) In an individual patient there exists a good correlation between AFP concentration in the serum and total AFP content in the tumor tissue. 4) The circulating amount of AFP is between 2.9 and 9.9 times higher than the tumor antigen content in the malignant tumor tissue. 5) Eight crystalline preparations of AFP isolated from tumor homogenate, plasma, ascites and pleural effusions of patients with hepatocellular carcinomas showed identical antigenic determinants. These results suggest an active elimination of AFP from the tumor cells into the serum. It is likely that the tumor antigen synthesized in malignant tissue and the AFP secreted in biological fluids have identical structures.

- 3277 SERUM- α_1 -FETOPROTEIN IN HEPATOCELLULAR CARCINOMA. (E.) Kohn, J. (Dept. Chem. Pathol., Queen Mary's Hosp., Roehampton, London, England) and P. C. Weaver. *Lancet* (7876):334-337, 1974.

Sera from 2225 patients, 107 with primary hepatocellular carcinoma and 2118 with other diseases, mainly hepatic disorders, were screened for α_1 -fetoprotein (AFP) in serum by a sensitive counter-current immunoelectrophoretic technique. The screening test detects serum-AFP at concentrations in the order of 200 ng. per ml. Ninety out of the 107 cases of hepatocellular carcinoma, including five cases of hepatoblastoma, were AFP positive, and four cases which were negative on screening were shown by radioimmunoassay (RIA) to have significantly raised serum-AFP levels. RIA does reveal a greater percentage of AFP-positive cases, but it also poses serious problems of interpretation; however, RIA is essential in monitoring progress and response to treatment, especially in hepatoblastoma and malignant teratoma. Raised AFP levels after surgery or chemotherapy indicate failure of treatment, though the converse does not necessarily apply. In malignant testicular teratoma, the frequency of raised serum-AFP was 32 out of 117 cases (27%). Significant amounts of AFP were found in nine cases of carcinoma other than hepatocellular. Raised AFP levels, usually transient and in most cases small, were found in 16 cases of liver disease other than hepatocellular carcinoma, and in 14 cases in which a diagnosis was not available. The frequency of false-positives was 1.8%. AFP detection and assay correctly performed and interpreted is a valuable, sensitive, and specific serological marker of

hepatocellular carcinoma. It is suggested that the AFP test be performed for those with cirrhosis, hemochromatosis and porphyria cutanea tarda, that is, patients with a high risk of liver cancer. The screening technique described seems to be adequate for the detection of hepatocellular carcinoma in most cases.

- 3278 HISTOLOGIC CHANGES IN LIVERS OF PYRIDOXINE-DEPRIVED BABOONS—RELATION TO α_1 FETOPROTEIN AND LIVER CANCER IN AFRICA. (E.) Foy, H. (Wellcome Trust Res. Lab., Nairobi, Kenya), A. Kondi, J. N. P. Davies, B. Anderson, A. Parker, J. Preston and F. G. Peers. *J Natl Cancer Inst* 53(5):1295-1311, 1974.

Histological changes occurring in the livers of 15 baboons fed a pyridoxine-deficient diet were observed. The purpose of the study was to assess any relation between these changes and the presence of α_1 fetoprotein (AFP) and their connection with the high incidence of primary liver cancer in humans in certain parts of Africa. Changes due to pyridoxine deprivation were compared with liver histologic changes in a second group of 15 animals fed the known carcinogen aflatoxin B₁. Ten baboons were intermittently fed a balanced artificial diet lacking only pyridoxine for 2 to 6 yr. Half developed increased amounts of AFP in their sera and had multiple atypical hyperplastic nodules regarded in some as neoplastic or premalignant. The animals had megaloblastosis and anisocytosis, multinucleosis, abnormal mitoses, liver cell plates more than 2 cells thick, and sheets of bile ductule cells; the combination suggests neoplasia. Five other baboons totally deprived of pyridoxine died within 6 to 8 months, with rapidly developing hepatocellular injury. None had atypical hyperplastic nodules, abnormal liver cell plates, increased bile ductule cells, AFP, or signs of tumor, probably because of early death. Fifteen other baboons were given aflatoxin B₁, accompanied, preceded, or followed by pyridoxine deprivation. Their liver changes were not as severe as those seen in the animals given the pyridoxine diet alone. This may be attributed to the stimulation of some immunologic mechanism. In all animals deprived of pyridoxine, the serum B₆ levels fell from a normal range of 200-350 ng/ml to 5-15 ng/ml, and increased tryptophan metabolites appeared in the urine. The fact that neither atypical hyperplastic nodules nor AFP was present in half the baboons, regardless of these low serum B₆ levels, suggests that pyridoxine deficiency does not produce its effects directly, and is possibly associated with differences in immunologic competence.

- 3279 EMBRYONIC ANTIGEN EXPRESSION ON 2-ACETYL-AMINOFLUORENE INDUCED AND SPONTANEOUSLY ARISING RAT TUMOURS. (E.) Baldwin, R. W. (Cancer Res. Campaign Labs., U. Nottingham, England) and B. M. Vose. *Br J Cancer* 30(3):209-214, 1974.

Embryonic antigens were detected at the surface of 2-acetyl-aminofluorene (AAF)-induced mammary and ear

duct carcinomas by the complement dependent cytotoxicity of sera from multiparous rats compared with that of virgin control sera. None of the sera had any reactivity against cells from adult liver, lung, diaphragm, or kidney. Similar tests with spontaneously arising sarcomas and mammary carcinomas gave comparable results, although only a low proportion of the multiparous rat sera were reactive. With both the spontaneous and AAF-induced tumors the cytotoxicity was variable and generally low. Indirect membrane immunofluorescence tests were performed using sera from multiparous rats against two AAF-induced and two spontaneously arising mammary carcinomas. No significant reaction was demonstrable against any of these tumors. In contrast, these sera showed a significant level of membrane staining against 4-dimethylaminoazobenzene-induced hepatomas and 3-methylcholanthrene-induced sarcomas. Re-expression of embryonal components may be a concomitant of neoplastic transformation.

3280 MEMBRANE MARKERS ON CHRONIC LYMPHOCYTIC LEUKEMIA CELLS: A B CELL LEUKEMIA WITH ROSETTES DUE TO ANTI-SHEEP ERYTHROCYTES ANTIBODY ACTIVITY OF THE MEMBRANE BOUND IgM AND A T CELL LEUKEMIA WITH SURFACE Ig. (E.) Brouet, J. C. (St. Louis Hosp. Paris, France) and A. M. Prieur. *Clin Immunol Immunopathol* 2(4):481-487, 1974.

Several membrane markers were used to classify the peripheral blood lymphocytes of two patients with chronic lymphocytic leukemia. More than 80% of the circulating lymphocytes of the first patient had a monoclonal membrane bound Ig μ k which was an actual cell product; a similar percentage of lymphocytes had a receptor for aggregated IgG. Only 12% of the cells were killed by anti-T antiserum, although nearly all cells exhibited rosette formation with sheep erythrocytes (SE) with a morular appearance of most rosettes. The rosette formation was unusual in that it took place under experimental conditions which do not usually allow the attachment of SE to T lymphocytes. The antigenic determinant of SE involved in this reaction was shared by Forssman-positive cat erythrocytes and was not detected on erythrocytes from Forssman-negative species. Guinea pig kidney extracts were able to inhibit the rosette formation and induce the redistribution of membrane bound Ig. The data in this case suggest a B cell proliferation with anti-SE activity of the monoclonal surface IgM. In the second patient, 90% of the cells bore membrane bound IgG λ . However, only 3% of the cells had a receptor for aggregated IgG, 70% of the cells were killed by an anti-T antiserum, and 40-60% of the cells formed rosettes with SE. After trypsinization and short-term culture, no Ig molecules synthesized *in vitro* could be demonstrated at the surface of the cells, although 30% of the cells still formed rosettes with SE. In this case, the data suggest that the leukemic cells were of T origin, although presumably monoclonal surface Ig was present on freshly drawn cells. The results underline the need for using several membrane markers to classify lymphoproliferative diseases.

3281 DIFFERENTIATION BETWEEN EARLY AND LATE MEMBRANE ANTIGEN ON HUMAN LYMPHOBLASTOID CELL LINES INFECTED WITH EPSTEIN-BARR VIRUS. I. IMMUNOFLOUORESCENCE. (E.) Ernberg, I. (Karolinska Inst., Stockholm, Sweden), G. Klein, F. M. Kourilsky and D. Silvestre. *J Natl Cancer Inst* 53(1):61-65, 1974.

Two serologically distinct components of Epstein-Barr virus (EBV)-specific membrane antigen were detected on human lymphoblastoid cell lines by the selective absorption of various EBV-positive sera from Burkitt's lymphoma and nasopharyngeal carcinoma patients. The early membrane antigen was detected on cells cultured in the presence of cytosine arabinoside which effectively blocked viral DNA synthesis and the synthesis of viral capsid antigen (VCA), whereas late membrane antigen was found almost exclusively on cells that had progressed to VCA synthesis. The blocking of direct conjugate binding to the cells by unconjugated sera was demonstrated.

3282 TUMOR-SPECIFIC MEMBRANE ANTIGENS IN ESTABLISHED CELL LINES FROM GLIOMAS. (E.) Wahlstrom, T. (III Dept. Pathol., U. Helsinki, Finland), E. Linder, E. Saksela and B. Westermark. *Cancer* 34(2):274-279, 1974.

Rabbits were immunized with lyophilized glioblastoma multiforme tissue from a tumor taken from a 38-yr-old man. After 4 months, at which time the animals suffered from severe encephalomyelitis, their sera were collected and absorbed with lyophilized human serum, and lung, liver, kidney, placenta, brain, and fresh HeLa cells until they reacted only with cell lines cultured from malignant gliomas in indirect immunofluorescence tests. The immunofluorescent staining of the glioma cell lines revealed three distinct patterns of membrane fluorescence. In some lines, a delicate segmentary type of fluorescence was seen only at the cell margin; others showed a coarse brush-like pattern. One glioma line had a fine fibrillary membrane fluorescence which extended to the thinnest dendritic extensions characteristic of this line. Each line displayed only one and always the same type of fluorescence in repeated tests and different passages *in vitro*. In a coded series of 23 cell lines derived from different normal and neoplastic tissues, all of the 15 glioma lines tested were correctly identified by their tumor-specific membrane antigens. The data suggest that these tumors bear common antigens which are either determined by the normal cell genomes or are acquired during the process of neoplastic transformation.

3283 FURTHER STUDIES ON MOUSE FETAL ANTIGEN CROSS-REACTIVE WITH RAUSCHER LEUKEMIA. (E.) Ishimoto, A. (Res. Inst., Aichi Cancer Ctr., Nagoya, Japan), Y. Suzuki, T. Yoshida and Y. Ito. *Cancer Res* 34(9):2338-2343, 1974.

The time course for the appearance of the embryonic cell surface antigen which cross-reacts with Rauscher

(3284-3286)

leukemia was examined. The indirect immunofluorescence test was used. The antigen detectable by test serum first appeared in 12-day-old mouse embryos and continued to be demonstrable until the day of birth. The antigen was abundant in cells from the digestive tract, but not in cells from the liver and brain. A natural antibody reactive to mouse fetal antigen(s) was shown to exist in the sera of a few C57BL/6 mice of both sexes older than 8 months. The antibody cross-reactive with Rauscher leukemia cells and embryonic cells was clearly differentiated from the IgM autoantibody in mouse alloantisera.

3284 STUDIES OF TUMOR-SPECIFIC AND HERPESVIRUS NONVIRION ANTIGENS. (E.) Hollinshead, A. (George Washington U. Sch. Med., Washington, D.C.), G. Tarro, W. A. Foster, Jr., L. J. Seigel and W. Jaffurs. *Cancer Res* 34(5):1122-1125, 1974.

Human cervical cancer sera absorbed with primary cancer cells did not react in delayed hypersensitivity reactions with herpesvirus nonvirion antigen or with cervical carcinoma-separated antigen. One of two cancer sera absorbed with herpesvirus type 2-infected HEp-2 cells proved to be anticomplementary, while the other serum reacted with the cervical cancer antigen. Although the soluble portions of the herpesvirus nonvirion antigens and the cervical cancer antigens were quite different in composition, they did have components of identity which were necessary for complement fixation (CF) reactivity. Three patients with Stage 2A epidermoid carcinoma of the cervix, Stage 1 endometrial adenocarcinoma, and Stage 1 breast cancer, who were not anergic to skin tests with mumps and streptokinase-streptodornase, were further skin tested with material eluted by polyacrylamide gel electrophoresis from Regions 1, 2, and 3 of the separated cervical cancer antigens and normal vaginal antigens. Positive tests were seen in the cervical cancer patient to the Regions 2 and 3, but not to the Region 1, of the cervical cancer antigens. Tests to all three regions were negative in the other two patients, and tests to all three regions of the normal vaginal antigens were negative in all three patients. Glycoproteins were present in Region 1, but absent from Regions 2 and 3. Cervical cancer gel Regions 3 were positive for CF reactivity with antisera specific for herpesvirus nonvirion antigens. Thus, cancer antigens share a common component with the nonvirion antigens, and this component is necessary for CF reactivity.

3285 HUMAN LEUKEMIA ANTIGENS: PARTIAL ISOLATION AND CHARACTERIZATION. (E.) Metzgar, R. S. (Duke U. Med. Ctr., Durham, N.C.), T. Mohanakumar, R. W. Green, D. S. Miller and D. P. Bolognesi. *J Natl Cancer Inst* 52(5):1445-1453, 1974.

Human leukemia-associated antigens detected by non-human primate antisera were freed from leukemia cells

by trypsin digestion, autolytic or spontaneous release, and KCL extraction; the released antigen was sedimented at 100,000 X g in 4-6 hr. Electron microscope studies revealed many membrane vesicles in the ultracentrifuged pellets. Of the three release methods, trypsinization was most effective. The leukemic cells after trypsin digestion were viable and yet refractory to lysis by nonhuman primate antisera to human leukemia cells. The antigenic sites were regenerated within 24 hr at either 37 or 4 C. High yields of soluble leukemia-associated and HL-A antigens were obtained by pronase treatment. These leukemia-associated antigens could not be sedimented at 60,000 X g for 16 hr and were detected in the included volume of Sephadex G-200 gel filtration. The Sephadex G-200 fractions possessing the leukemia-associated antigens specific for lymphatic leukemia cells also contained HL-A12 activity. Neuraminidase treatment of leukemic cells resulted in a complete loss of leukemia-associated antigen activity from these cells. However, no antigen activity could be recovered in the supernatant after such enzyme digestion. Neuraminidase treatment of the subcellular membrane antigens isolated by tryptic digestion and the soluble antigens prepared by pronase digestion had no effect on the ability of these preparations to inhibit the leukemia antisera.

3286 IMMUNOGENETIC ASPECTS OF NASOPHARYNGEAL CARCINOMA: I. DIFFERENCES IN HL-A ANTIGEN PROFILES BETWEEN PATIENTS AND CONTROL GROUPS. (E.) Simons, M. J. (WHO Immunol. Res. Training Ctr., Dept. Path., U. Singapore), G. B. Wee, N. E. Day, P. J. Morris, K. Shanmugaratnam and G. B. De-The. *Int J Cancer* 13(1):122-134, 1974.

Preliminary analysis of HL-A antigen patterns in 393 subjects showed a higher frequency of undetectable second locus antigens (particularly HL-A13 and W10) in 28 Singapore Chinese patients with nasopharyngeal carcinoma (NPC) compared with 175 Chinese, 104 Malays, and 86 Indians without NPC. The same phenomenon was demonstrated in a study of 136 NPC patients (74 Singapore Chinese, 14 Hong Kong Chinese, 28 Malaysian Chinese, 12 Malays, 7 Kadazans, and 1 Dyak) and 61 Singapore Chinese without NPC. In this study, the significance of the second locus difference between Chinese with NPC and Chinese controls was increased 10-fold. Additionally, the frequency of HL-A2 was significantly higher among the NPC patients. Both the elevation of HL-A2 frequency and the deficit of detectable second locus antigens remained significant after application of the most conservative correction factor for the number of antigens investigated. The increase in HL-A2 was represented by the first locus component in Chinese NPC patients and by the second locus component in non-Chinese NPC patients. The lack of second locus antigens could be either a result of NPC or a genetic marker of susceptibility to the development of the malignancy.

3287 TUMOR GROWTH IN THE GUINEA PIG: ALPHA GLOBULIN CHANGES ASSOCIATED WITH LYMPHOCYTE SUPPRESSION. (E.) Lilley, D. P. (John L. Smith Mem. Ctr. Cancer Res., Maywood, N.J.), D. R. Burger and R. M. Vetto. *J Natl Cancer Inst* 53(3):701-709, 1974.

Serum globulin changes associated with tumor growth and suppressed lymphocyte responsiveness to mitogen stimulation were observed in strain-13 guinea pigs. Disc gel electrophoresis of serum harvested during growth of a transplanted, 3-methylcholanthrene-induced fibrosarcoma showed an increase in globulin fraction 4 in the α -globulin region. Globulin fraction 4 significantly rose by 16 days of tumor growth and remained elevated until the animals died. Concomitant with this increase, *in vitro* suppression of lymphocyte reactivity to phytohemagglutinin and pokeweed mitogen was observed. Inhibition, measured by the level of ^3H -thymidine incorporated into whole blood cultures, increased in severity until the animals died. Direct correlations between progressive tumor growth, suppression of cell-mediated tumor immunity, and increases in disc gel fraction 4 were observed. A regulation of immune responsiveness in a progressively growing tumor system may compromise cell-mediated immune responses which seem necessary for tumor destruction.

3288 ACTIVITY OF RNA STRUCTURES IN A SEROLOGICAL REACTION APPLIED TO STUDY TUMORS.

(It.) Guarini, G. (Piedmont Inst. Exp. Zoonosis Prevention, U. Turin, Italy), P. Lovisetto, V. Biarese and G. Molfese. *Tumori* 60(3):251-253, 1974.

A test, similar to the complement-fixation test, was run on sera from 586 normal controls, 904 patients with neoplasms and 1008 patients with non-neoplastic disease. 0.5 ml of serum, diluted 1:10 with pH 7.2 sodium veronal buffer, was incubated for 30 min at 37 C with 0.3 ml of solution containing RNA from a mutant of *Saccharomyces cerevisiae* (160-200 $\mu\text{g}/\text{ml}$) in the same buffer. Then 0.5 ml of sheep RBC was added, and results were read after reincubation at 37 C for another 30 min. Complement-fixation tests were run simultaneously. This serological test was positive on 83% of the controls, 32.3% of patients with neoplasms, and 65.3% of patients with non-neoplastic diseases. Electrophoretic examination of control sera which had been incubated with this RNA showed, in many cases, a β -globulin band, while no change was noted in a large percentage of sera from patients with malignant neoplasms. The difference was statistically significant. Two explanations are possible for this phenomenon. A serum factor, present in most of the controls and absent in most patients with neoplasms, might undergo an immunological reaction with specific structures having an antigenic function. This is supported by previous studies in which negative reactions were obtained in umbilical cord blood; positive results increased with age, and adult levels were reached at age 2 yr. Alternatively, this serological reaction may be due to the transformation of β -1-C into β -1-A in the C_3 fraction of complement when normal serum is incubated with RNA from *S. cerevisiae*.

3289 CELL-MEDIATED IMMUNE STATUS OF BREAST CANCER PATIENTS: EVALUATION BY SKIN TESTS, LYMPHOCYTE STIMULATION, AND COUNTS OF ROSETTE-FORMING CELLS. (E.) Nemoto, T. (Dept. Breast Surg., Roswell Pk. Mem. Inst., Buffalo, N.Y.), T. Han, J. Minowada, V. Angkur, A. Chamberlain and T. L. Dao. *J Natl Cancer Inst* 53(3):641-645, 1974.

Immunologic evaluations involving lymphocyte counts, skin tests with common antigens, counts of rosette-forming T cells, and determinations of lymphocyte blastogenesis were performed on eight women with benign breast diseases, 13 women with localized breast disease undergoing treatment, 27 women with metastatic breast disease undergoing treatment, and seven women with terminal breast cancer. The breast cancer patients showed no impairment of cell-mediated immunity except in the very late stage of metastatic disease. Impairment in the terminal stage was demonstrated by skin tests and less clearly by lymphocyte stimulation with phytohemagglutinin or common antigens, but not by lymphocyte counts or counts of rosette-forming cells. The data indicate a reasonably good correlation between skin tests and blastogenic response. The gradual progression of breast cancer is apparently not reflected by immunologic tests, since the patient's cell-mediated immunity seems to remain intact until the late stage of the disease.

3290 IMMUNOGLOBULIN ANALYSIS OF C57BL MICE INFECTED WITH A RADIATION-INDUCED LEUKEMIA VIRUS. (E.) Sassen, A. (Dept. Radiobiol., CEN/SCK, Brussels, Belgium), F. V. Plaetse, M. Janowski and J. R. Maisin. *J Natl Cancer Inst* 52(2):539-543, 1974.

C57BL mice infected with a radiation leukemia virus [RadLV(D)] that was inoculated either as a cell-free extract or as a cell suspension displayed serologic modifications. Total immunoglobulin concentration, as determined by the radial immunodiffusion technique, increased considerably within 40-50 days in mice injected with 1.5×10^7 cells, reached a plateau, and thereafter decreased. The IgG2a and IgM immunoglobulins were changed most markedly and monoclonal paraprotein was not observed. The changes in immunoglobulin concentration did not directly parallel the increase in spleen weight observed in the treated mice, although both parameters were determined by the number of cells injected and the interval after inoculation. Despite a high immunoglobulin level, the humoral immune response of the treated mice was depressed. Leukemic spleen cells prepared at various intervals after the *in vivo* injection of the virus extract showed a greater *in vitro* incorporation of labeled amino acids into cellular proteins than did normal cells. There was no correlation between the rate of incorporation and the time after virus injection; in contrast, the excretion of labeled proteins by the leukemic cells decreased with time. By immunofluorescence, murine leukemia virus antigens were detected in cells which were also positive for immunoglobulin synthesis.

- 3291 INHIBITION OF LEUKOCYTE MIGRATION BY TUMOR-ASSOCIATED ANTIGENS IN SOLUBLE EXTRACTS OF HUMAN BREAST CARCINOMA. (E.) McCoy, J. L. (Litton Bionetics, Ins., Kensington, Md.), L. F. Jerone, J. H. Dean, G. B. Cannon, T. C. Alford, T. Doering, and R. B. Herberman. *J Natl Cancer Inst* 53(1):11-17, 1974.

Human leukocyte preparations were used in leukocyte migration-inhibition (LMI) assays to identify tumor-associated antigens (TAA) of human breast carcinomas. Tests were done on leukocytes from patients with breast carcinoma, benign breast disease, and cancer of other sites. Normal controls were also tested. Antigens were obtained by 3M KCL extraction of breast carcinoma, benign breast tissues, and normal breast tissues. Most tests were allogeneic; two were autologous. Migration of leukocytes from 20/26 breast carcinoma patients was markedly inhibited by KCL extracts of breast carcinoma. No leukocytes tested by the LMI assay against KCL extracts of normal or benign breast tissue were significantly inhibited. Infrequently, leukocytes of patients with carcinoma of other sites were inhibited by soluble KCL extracts of breast carcinoma. Allogeneic reactions suggested that different breast carcinomas had common antigens.

- 3292 CYTOGENETIC STUDY OF HUMAN LYMPHOID T-CELL LINES DERIVED FROM LYMPHOCTIC LEUKEMIA. (E.) Huang, C. C. (Springville Labs., Roswell Park Mem. Inst., Springville, N.Y.), Y. Hou, L. K. Woods, G. E. Moore and J. Minowada. *J Natl Cancer Inst* 53(3):655-660, 1974.

The chromosomes of lymphoid cell lines with characteristics of thymus-derived lymphocytes (T cells), established from the blood of one female patient and one male patient with acute lymphoblastic leukemia were studied. Both patients had had intensive courses of chemotherapy. The primary blood culture of the female patient had a pseudodiploid mode with characteristic markers; only a few cells were normal diploid. Eight cell lines were established from this patient. Shortly after establishment, all eight lines had the same predominant karyotype as the primary culture. Several months later, five lines lost T-cell characteristics and had characteristics of lymphocytes derived from the bone marrow, B cells. At the same time, their karyotype became normal. The B cells with diploid karyotype may have represented a selection of normal lymphocytes that were always present in the patient as well as in the cultures. Two lines were lost in handling. Only one line had T-cell characteristics, with a consistent pseudodiploid karyotype, 14 months after establishment. These cells with T-cell markers were probably leukemic. Trypsin and Giemsa banding study revealed the detailed rearrangements and the derivation of the markers in the pseudodiploid karyotype. The cell line from the male patient had a modal chromosome number of 47 two to four months after establishment but a hypertetraploid mode after 11 months *in vitro*. The origin of the chromosome abnormalities of these cultures is unknown.

- 3293 IMMUNOGLOBULIN-SECRETING TUMORS IN THE LOU/WSL RAT: STUDY OF 200 IMMUNOCYTOMAS. (Fr.) Bazin, H. (Fac. Med., Catholic U. Louvain, Belgium). *Ann Immunol (Inst Pasteur)* 125C(1/2):277-279, 1974.

Immunoglobulins secreted by 200 ileocecal immunocytomas in LOU/Wsl rats were studied. The monoclonal immunoglobulins secreted were mainly of the IgE type, and the frequency of the other types decreased in the order IgG1, IgG2a, IgG2c, IgM, IgG2b and IgA. This distribution of immunoglobulins differs greatly from that found in plasma cell tumors induced in BALB/c mice. LOU/Wsl rats are characterized by a high incidence of spontaneous immunocytomas, which can be readily transplanted and maintain their secretory properties during *in vitro* and *in vivo* passage. In LOU/Wsl rats, the incidence of λ type tumors was low, and all Bence-Jones proteins were of the κ type.

- 3294 ANALYSIS OF LYMPHOCYTE STIMULATION BY LECTINS AND LECTIN DERIVATIVES. (E.) Cunningham, B. A. (Rockefeller U., New York, N.Y.). *Biomed Perspect Agglutinins Invertebrate Plant Origins* 234:219-225, 1974.

The mitogenic lectins, particularly concavavalin A (Con A) have been used to study the initial events required at the cell surface for the stimulation of mitosis in lymphocytes. Since the mechanisms by which Con A exerts its various biological activities on lymphocytes may depend on its molecular size, shape, organization of subunits, and the number and type of binding sites, the structure of the protein must be known in detail. Treatment of Con A with succinic anhydride produces succinyl-Con A, a lectin which at pH 7.4 has the same specificity but differs in charge and has half the valence of native Con A. Both lectins bind to lymphocytes and erythrocytes, but with mouse lymphocytes Con A can exhibit two antagonistic properties not shown by succinyl-Con A: the ability to induce cap formation with its own receptors; and the ability to restrict the mobility of ligand receptor complexes such as anti-Ig plus cell surface Ig molecules, or Con A plus its glycoprotein receptors. The combination of anti-Con A and bound succinyl-Con A has properties similar to those of Con A. These abilities are probably more critically dependent on valence than on the net charge. Both lectins are equally effective mitogens, they both show maximal stimulation in concentrations as dilute as 6 μ g/ml. Observations indicate that the process of capping is not required for mitogen stimulation. The increased negative charge of the succinyl derivative may be more critical than its valence in its ability to prevent cell death. The valence of the lectin appears to play an important role in the modulation of the mobility of lymphocyte surface receptors, but the net charge may be equally important in the inhibition of mitogenesis at high lectin concentrations. Mitogenic lectins, unlike non-mitogenic lectins, may be able to bind surface receptors which are attached to a postulated system of chochicine-binding proteins.

- 3295 BULLOUS PEMPFIGOID IN CHRONIC LYMPHOCYTIC LEUKEMIA WITH THE DEMONSTRATION OF ANTI-BASEMENT MEMBRANE ANTIBODIES. (E.) Cuni, L. J. (Queens Hosp. Ctr., Jamaica, N.Y.), H. Grunwald and F. Rosner. *Am J Med* 57(6):987-992, 1974.
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- 3297 INDUCTION OF MARKED HYPERGAMMAGLOBULINEMIA WITH XINOGENIC TUMORS IN HAMSTERS: IMMUNOPATHOLOGIC STUDIES. (E.) Ve Richman, A. (Wistar Inst. Anat., Biol., Philadelphia, Pa.) and V. Defendi. *J Immunol* 112(6):2241-2250, 1974.
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- 3303 SURFACE IMMUNOGLOBULINS ON MOUSE MYELOMA CELLS. (E.) Princler, G. L. (Natl. Cancer Inst., Bethesda, Md.) and K. R. McIntire. *Cell Immunol* 15(1):197-207, 1974.
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- 3307 ATTEMPTS TO INDUCE CULTURES OF BALB/c MYELOMA AND P3-J BURKITT'S LYMPHOMA CELLS TO PRODUCE SPECIFIC PHAGE NEUTRALIZING ANTIBODY. (E.) Krueger, R. G. (Dept. Microbiol., U. Washington, Seattle), A. C. Watkins and L. E. Volkman. *J Immunol* 112(4):1415-1419, 1974.
- 3308 SPECIFICITY OF IMMUNE LYMPHOCYTES FOR *IN VITRO* DETECTION OF TUMOR SPECIFIC TRANSPLANTATION ANTIGENS. (E.) Harris, L. F. (Sch. Med., Ohio State U., Columbus), V. V. Hamparian, J. H. Hughes, H. G. Cramblett, E. A. Young and K. L. Fowler. *J Reticuloendothel Soc* 15(6):12a, 1974.
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- 3377 SPONTANEOUS REGRESSION OF THE SHOPE PAPILLOMA: RELATIONSHIP OF LEUCOCYTIC INFILTRATION AND TUMOR CELL PROLIFERATION. (E.) Kreider, J. W. (Coll. Med., Pennsylvania State U., Hershey) and B. A. Beltz. *Proc Am Assoc Cancer Res* 15(March):128, 1974.

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See also:

* (Rev): 3012, 3016, 3023, 3024

* (Chem): 3047, 3140, 3141

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- 3380 CYSTADENOFIBROMA OF THE OVARY: A CLINICO-PATHOLOGIC STUDY OF 34 CASES AND COMPARISON WITH SERIOUS CYSTADENOMA. (E.) Czernobilsky, B. (Kaplan Hosp., Rehovot, Israel), R. Borenstein and M. Lancet. *Cancer* 34(6):1971-1981, 1974.

Clinical and pathologic features of 34 cases of ovarian cystadenofibroma were compared with those of 39 serous cystadenofibromas. The clinical features were similar in both. Pathologic differences were the following: papillary projections of cystadenofibromas were short, broad, firm structures, frequently hyalinized, those of cystadenomas were slender, delicate and friable with less frequent hyalinization. The epithelial elements of all the cystadenomas were unequivocally benign, while in the cystadenomas there were epithelial tufting, mitoses, atypia, and in three cases borderline malignancy. The histogenesis of cystadenofibromas is from germinal epithelium and underlying stroma. It is concluded that ovarian cystadenofibroma is more common than generally believed and is entirely benign. It should be classified as a distinct entity.

- 3381 CHANGES IN THE STROMA OF THE UTERUS IN EXPERIMENTAL GLANDULAR-CYSTIC HYPERPLASIA OF THE ENDOMETRIUM. (Rus.) Antipova, L. M. (I. P. Pavlov 1st Leningrad Med. Inst., USSR). *Arkh Patol* 35(9):45-49, 1972.

Changes in the vaginal and uterine stroma were studied in female golden hamsters: 40 were oophorectomized and then given diethylstilbestrol dipropionate (0.1 mg/g/day for 150 days). Controls consisted of 26 oophorectomized and 40 intact hamsters. Animals were sacrificed after five to 150 days. In experimental animals glandular-cystic hyperplasia of the endometrium developed in the uterine horns, with signs of epithelial atypism becoming evident late in the experiment. Proliferation and hyperkeratosis of the squamous epithelium was noted in the vagina and cervix. The vaginal stroma became fibrotic, while that in the uterine horns was characterized by edema and stromal proliferation with no evidence of fibrosis. Increases in the number of eosinophils occurred in the vagina and cervix, while in the endometrial stroma plasma cell infiltrates were the most typical finding. These changes produced by hormone treatment are considered to be indicative of the establishment of humoral and cellular immunity.

- 3382 SPONTANEOUS MALIGNANT LYMPHOMA IN A NEW-WORLD PRIMATE. (E.) Page, R. C. (Dep. Pathol., Univ. Washington, Seattle), L. Schectman, W. F. Ammons, and L. Dillingham. *Vet Pathol* 11(1):52-59, 1974.

Spontaneous occurrence of a disease with many features consistent with malignant lymphoma was observed in a cotton-top marmoset (*Saguinus oedipus*). The animal had generalized lymphadenopathy and died following administration of anesthetic; its organs were examined grossly and microscopically. Grossly, the

lymph nodes were enlarged two- to four-fold, exhibited a glistening capsule, and bulged on the cut surface; the liver had a faint reticular pattern on the cut surface; the spleen was enlarged three-fold with small yellowish nodules; the adrenals were enlarged. Microscopically, an infiltrate of primitive reticular cells was observed in the liver, kidneys, adrenals, lymph nodes, spleen, bone marrow, and lungs. Cells of the same type made up 20-30% of leucocytes in the circulating blood and varied in size (9-20 μ m). The alterations observed in the animal were indicative of a hematopoietic neoplasm, lymphogranuloma, an immunopathologic process, or some combination of those. Most of the unusual pathologic features were similar to those previously seen in viral-induced malignancy in animals of same species, supporting a diagnosis of lymphosarcoma of the reticulum cell type.

- 3383 GIANT CELL NEOPLASMS OF THE JAWBONES AND THE CONCEPT OF "BROWN TUMOR". (Ger.) Bonk, U. (Nymphenburg Inst. Pathol., Munich, Germany). *Verh Dtsch Ges Pathol* 58:466-470, 1974.

The change of meaning of the term "brown tumor" is illustrated on the basis of a literature review, and a retrospective study was made of 25 earlier cases with clinical and pathological diagnosis of "brown tumor". Histological studies of biopsies from the 25 cases diagnosed as brown tumors revealed juvenile bone cysts in seven cases, giant cell tumor in six, aneurysmal bone cysts in four, and nonossified fibroma, hyperparathyroidism, giant cell reaction of the hand bones, and unknown diagnosis in two cases each. This proves the term "brown tumor", which represents no unique bone disease, has lost its prognostic importance. The histological characteristics for differentiating between giant cell tumor and central giant cell granuloma of the jaws cannot be fully confirmed.

- 3384 THE HISTOGENESIS, HORMONAL ACTIVITY AND THE MALIGNANT POTENTIAL OF BRENNER TUMORS. (Ger.) Paulussen, F. (Gynecol. Obstet. Clin., Univ. Bonn, Germany) and U. D. Koenig. *Geburtshilfe Frauenheilk* 34(6):463-467, 1974.

The histogenesis, hormonal activity, and malignant potential of Brenner tumors are discussed on the basis of two cases. A typical Brenner tumor with cystic changes and pseudomucinous epithelial transformation was found in a 68-yr-old patient. No evidence of malignancy was found. Investigations of the vaginal smear and endometrium suggested estrogen production by the tumor. A slight degree of endometrial hyperplasia was found. A malignant Brenner tumor associated with a papillary adenocarcinoma of the endometrium was found in another 76-yr-old patient. This is the 35th case of malignant Brenner tumor, and the second case of malignant Brenner tumor associated with carcinoma of the endometrium in the literature. No hormonal activity was demonstrated in the vaginal epithelium or in the endometrium.

- 3385 THYMIDINE KINASE AND THYMIDYLATE SYNTHETASE ACTIVITY IN NORMAL INTESTINAL CELLS AND NEOPLASTIC LESION OF THE COLON. (E.) Peterson, A. (Mem. Sloan-Kettering Cancer Ctr., New York, N.Y.) and M. Lipkin. *Proc Am Assoc Cancer Res* 15(March):28, 1974.
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- 3398 ACUTE GRANULOCYTIC LEUKEMIA IN CATS. (E.) Fraser, C. J. (M. D. Anderson Hosp., Tumor Inst., Houston, Tex.), G. N. Joiner, J. H. Jardine and C. A. Gleiser. *J Am Vet Med Assoc* 165(4):355-359, 1974.
- 3399 THE MINERALIZING ORGANIC MATRIX OF THE BENIGN CALCIFIED EPITHELIOMA OF MALHERBE. (E.) Nusgens, B. (Baviere Hosp., Liege, Belgium) and C. M. Lapiere. *J Cut Pathol* 1(1):47-53, 1974.
- 3400 PRECANCEROUS LESIONS OF THE LARYNX. (E.) Friedmann, I. (Northwick Park Hosp., Middlesex, England). *Can J Otolaryngol* 3(4):528-542, 1974.
- 3401 LARYNGEAL KERATOSIS AND ATYPIA. (E.) Fechner, R. E. (Baylor Coll Med., Houston, Tex.). *Can J Otolaryngol* 3(4):516-521, 1974.
- 3402 HAIRY CELL LEUKEMIA: CLINICAL, LIGHT- AND ELECTRON-MICROSCOPIC FINDINGS. (Ger.) Dullmann, J. (St. Georg Hosp., Hamburg, Germany), U. Wulfhekel, S. Drescher and K. Hausmann. *Dtsch Med Wochenschr* 99(17):859-863, 1974.
- 3403 ULTRASTRUCTURE OF SARCOMA 180. (E.) Yamamoto, I. (Kitasato U. Sch. Hygienic Sci., Kanagawa, Japan) and M. Takahashi. *J Electron Microsc (Tokyo)* 23(3):214, 1974.
- 3404 ULTRASTRUCTURE OF SEROSAL SURFACE IN GASTRIC CARCINOMA. (E.) Kondo, K. (Ctr. Adult Diseases, Osaka, Japan) and T. Nagatomo. *J Electron Microsc (Tokyo)* 23(3):147-159, 1974.

See also:

- * (Rev): 3010, 3013, 3029
- * (Viral): 3196, 3239
- * (Immun): 3343

3405 THE USE OF QUESTIONNAIRES IN DETECTING
PRETUMOR AND TUMOR LESIONS AMONG RAILWAY
PERSONNEL. (Rus.) Tsukerman, I. M. (Joint Railway
Hospital of the Odessa-Kishinev Railway, USSR),
V. K. Stezhkovoi and B. N. Boirsiuk. *Vopr Onkol*
20(5):67-72, 1974.

Questionnaires have been used since 1970 to detect premalignant and malignant diseases of the female genitalia, gastrointestinal tract and lung among railway workers and their families. The poll involved 18,627 males and 23,688 females. The largest age group was 40-49 yr (23%) among males and 30-39 (21.2%) among females. Analysis of symptoms revealed 8,124 persons with possible cancer or precancer (3,519 males and 4,605 females). Medical examination of potential cases revealed that 84 persons (43 males and 41 females) actually had malignant tumors. Among males the frequency of stomach, intestine and lung cancer was 0.5%, 0.4% and 0.4%, resp. and among females 0.2%, 0.2% and 0.1%, resp. The frequency of carcinoma of the female genitalia was 0.4%. Of 84 patients, 62 had curable tumors. There were 711 cases of precancer (213 males and 498 females) with stomach, intestine and lung involvement amounting to 2.6%, 1.8% and 2.1%, resp. among males and 1.8%, 1.6% and 1.1% among females. Diseases other than oncological ones were found in 1,202 of the subjects examined.

3406 FAMILIAL BREAST CANCER IN A NORMAL POPULATION. (E.) Lynch, H. T. (Creighton U. Sch. Med., Omaha, Neb.), H. Guirgis, S. Albert and M. Brennan. *Cancer* 34(6):2080-2086, 1974.

Observations of cancer occurrences, particularly carcinoma of the breast, in the families of more than 4000 consecutively ascertained normal subjects were evaluated independently at two medical centers. The sample consisted of 3261 patients at Omaha and 1058 patients at Detroit; results were extremely similar. The distribution of cancer of all anatomical sites in first-degree relatives of families of participants indicated that approximately one-half of all families did not manifest cancer; approximately one-third had cancer in a single first-degree relative; and slightly more than 20% had cancer in two or more first-degree relatives. Only 7% had cancer in three or more first-degree relatives. Approximately 9.1% of the lineages in the Omaha group and 7.4% of the Detroit lineages had a single member with breast cancer, while approximately 0.7% of lineages in both groups had two or more first-degree relatives with breast cancer. Familial associations were found between carcinoma of the breast and prostate, colon, ovary, endometrium, brain, and skin, within lineages. However, the only statistically significant association was found between carcinoma of the breast and the prostate ($p < 0.005$ for both groups combined). It is speculated that this association is related to hereditary factors involving specific variations in gonadal hormone production, chemical alterations, or aberrations in the response of the target organ to hormones. All these mechanisms and/or their interaction may be of etiologic importance.

3407 EPIDEMIOLOGY OF ADENOCARCINOMA OF THE KIDNEY. (E.) Wynder, E. L. (American Hlth. Fdn., New York, N.Y.), K. Mabuchi and W. F. Whitmore, Jr. *J Natl Cancer Inst* 53(6):1619-1634, 1974.

Etiologic factors of adenocarcinoma of the kidney were identified through a literature review and a case-control study. The case-control study was conducted on 202 patients (129 men and 73 women) with renal adenocarcinoma and 394 controls matched for sex, age, race, and hospital. The study showed a significant but moderate association between cigarette smoking and renal adenocarcinoma; the overall relative risk for cigarette smokers was 2.0 in males and 1.5 in females. Relative risks increased with an increase in the number of cigarettes smoked/day and were greater for males less than 50 yr of age than for those over 50 yr. Male cases indicated a significantly larger proportion of persons with a history of myocardial infarction (7%) than did controls (1%). Female cases contained a greater proportion of obese (at least 25% overweight) persons (28.8%) than did their controls (10.1%). Female renal adenocarcinoma cases included a smaller percentage of individuals who had never married than their controls; no differences were found related to reproductive variables such as parity. No significant relationships with coffee drinking, alcohol consumption, or occupational exposure could be determined. As a working hypothesis from these data, it is suggested that dietary factors, possibly related to a fat and/or cholesterol intake, are involved in the pathogenesis of renal adenocarcinoma.

3408 AN EPIDEMIOLOGIC STUDY OF BREAST CANCER. (E.) Henderson, B. E. (U. Southern California Sch. Med., Los Angeles), D. Powell, I. Rosario, C. Keys, R. Hanisch, M. Young, J. Casagrande, V. Gerkins and M. C. Pike. *J Natl Cancer Inst* 53(3):609-614, 1974.

A total of 308 California breast cancer patients under 65 yr of age participated in a case-control study of breast cancer. The patients and controls did not differ in terms of marital status or religion, but did differ in terms of age at first delivery, number of pregnancies, age at menarche, maternal age at delivery, and paternal age at delivery. The patients and controls showed little difference as to whether they were breast fed or had lactated. The incidence of breast cancer was more than 3-fold higher among first-degree relatives of the cancer patients compared with those of the controls. There was also a small excess of other types of cancer among the relatives of the cancer patients. A history of diabetes was obtained from 2.6% (8/308) of the cancer patients and (14/308) of the matched controls; this difference was not apparent among family members. The data are incompatible with the horizontal transmission of a human breast cancer virus through human milk. The familial aggregation of the disease did seem related to an altered state of estrogen metabolism or excretion, however, and a decreased risk of breast cancer was associated with hormone administration at natural menopause.

- 3409 EPIDEMIOLOGIC COMPARISON OF BREAST CANCER PATIENTS WITH EARLY AND LATE ONSET OF MALIGNANCY AND GENERAL POPULATION CONTROLS. (E.) Craig, T. J., (Sch. Med., Johns Hopkins U., Baltimore, Md.), G. W. Comstock, and P. B. Geiser. *J Natl Cancer Inst* 53(6):1577-1581, 1974.

A cross-sectional survey of 134 persons with a history of breast cancer and 260 community controls examined which of several postulated risk factors significantly differentiate breast cancer cases from age-matched controls selected randomly from the general population, and which, if any, of these factors show different patterns among early-onset and late-onset breast cancer patients. An increased risk of breast cancer associated with a positive family history for breast disease and with the experience of first childbirth at age 25 or older was confirmed. An increased risk was also associated with lactation. The first two risk factors were significantly associated with early onset cases only, while the third was associated only with late onset cases. This evidence supports the hypothesis that the pathology of breast cancer may be mediated by two biological mechanisms, the early-onset type with predominantly genetic etiology and the late-onset type being more related to socio-environmental factors. Parity, use of hormones, age at menarche, menopause, hysterectomy, or history of thyroid disease showed no association with risk of breast cancer.

- 3410 CHORIOCARCINOMA IN IBADAN, NIGERIA: EPIDEMIOLOGIC ASPECTS. (E.) Junaid, T. A. (U. Coll. Hosp., Ibadan, Nigeria), J. P. de Hendrickse, B. Oladiran, G. M. Edington and A. O. Williams. *J Natl Cancer Inst* 53(6):1597-1602, 1974.

Epidemiologic aspects of choriocarcinoma in Ibadan, Nigeria, were investigated through the analysis of specimens from surgical biopsy and of tissue from necropsies. Choriocarcinoma was diagnosed in 188 (66%) of 285 surgical biopsy specimens (all those registered as malignant trophoblastic disease) from Nigerian women. During a 12-yr period from 1960-1971, the Cancer Registry of the Pathology Department found choriocarcinoma to have a ratio frequency of 2.2%, making it the third most common malignant tumor among Nigerian females. The autopsy ratio for choriocarcinoma was 1:89. Peak age frequency (161 of 188 cases) was 21-40 yr, the peak periods of childbearing in the population. From tissue of 100 necropsies, the uterus was found to be the most common site (75%) of primary growth of choriocarcinoma. Hematogenous metastases were widespread, and an increased aggregation of mononuclear cells was observed around both primary and metastatic tumor deposits. An absence of primary uterine tumor was reported in 12 autopsies. An immunologic disturbance in patients with choriocarcinoma is suspected. However, the etiology of trophoblastic neoplasia and possible etiologic roles of factors such as malnutrition, consanguinity, and infective agents in Nigeria are not known.

- 3411 TYPE B VIRUS AND HUMAN BREAST CANCER. (E.) Henderson, B. E. (U. Southern California Med. Sch., Los Angeles). *Cancer* 34(4):1386-1389, 1974.

In recent years, virus-like particles have been observed in milk from women with a family history of breast cancer. Reverse transcriptase enzymatic activity characteristic of RNA tumor viruses also was found in the same milk specimens. This laboratory evidence suggesting milk transmission of a human breast cancer virus conflicted with prior epidemiologic data which indicated no increased breast cancer risk associated with the maternal line or with being breast fed. On the assumption that a milk agent could be etiologically important in breast cancer with onset at a young age, the epidemiologic factors relating to possible maternal transmission were reevaluated. Thus, this case-controlled study confirmed earlier observations. In addition, more recent laboratory studies have not shown a consistent relationship between the detection of virus-like particles in human milk and a history of breast cancer. If viruses are involved in the etiology of human breast cancer, vertical transmission through genetic mechanisms seems more consistent with available data. A total of 317 breast cancer patients and controls were interviewed and divided into groups by age at diagnosis: those less than 40 yr and those 40-59 yr. Regardless of age at diagnosis, breast cancer cases and controls did not differ in history of being breast fed. There was also no difference in the history of breast cancer in paternal compared to maternal aunts of both groups of breast cancer cases.

- 3412 EPIDEMIOLOGICAL STUDY ON PEPTIC ULCER AND GASTRIC CANCER IN THE CHINESE. (E.) Sung, J. L. (National Taiwan U. Hosp., China), T. H. Wang, T. H. Lu, S. C. Wu, T. W. Hsu and T. H. Lee. *Rev Gastroenterol* 6(2):111-115, 1974.

A mass survey was carried out on the epidemiology of diseases of the upper gastrointestinal tract in the Chinese, in addition to the detection of symptomless gastric cancer. Examination was made of 1367 government employees in Kaohsiung and 3464 government employees of the Taiwan Provincial Government. A first screening method was indirect x-ray fluorophotography of six different positions. Suspected cases were further studied in a hospital by direct x-ray fluorophotography, gastroscope photography, fiberoptic, fiberoptic biopsy, and fiberoptic cytology. Of these 4831 subjects, peptic ulcer was found to be the main disease in the organ system. Its incidence was 11.8% in the first group and 8.5% in the second group; the ratio of duodenal ulcer to gastric ulcer was 3:1 in the first group and more than 2:6 in the second group. Three cases of gastric cancer were detected (0.09%) in the second group (out of 3464 cases), one of which was superficial (early cancer). Comparison between this study and an earlier gastric x-ray mass survey of 1,500,000 subjects in Japan indicated that age-adjusted death rate as well as morbidity rate for gastric cancer in Chinese is nearly one half of that of the Japanese.

- 3413 EPIDEMIOLOGY OF STOMACH CANCER IN DAGESTAN.
(Rus.) Dalgat, D. M. (Dagestan Med. Inst., USSR), R. G. Aliev, G. I. Gireev and M. M. Abdulgamidov. *Vopr Onkol* 20(2):76-81, 1974.

Stomach cancer was diagnosed in 964 patients, 517 males (52.5%, 19.1 per 100,000) and 447 females (47.5%), between 1966 and 1970. In Dagestan the male to female ratio was 1.1:1.0. The highest incidence of stomach cancer was in the 60-69 yr age group (88.1 per 100,000) and the lowest in those under 29 yr (0.2 per 100,000). Specific attention was paid to elucidating the environmental factors and eating habits in the areas with abnormally high incidence of the disease (3 mountainous regions with incidences of stomach cancer 32.0, 34.0 and 40.0 per 100,000 resp. where 200 patients and 250 healthy adults were studied). Correlations between adverse eating habits and smoking and stomach cancer were confirmed. In particular, spiced food, pickles, fish, smoked products, overdone meat and excessive use of alcohol contributed to the disease. 74% of the patients had a history of precancerous diseases (peptic ulcers, gastritis, gastric polyposis). Soil and vegetation tests in areas with the highest incidence of stomach cancer showed excessive copper, cobalt, zinc, iron, boron, manganese and iodine.

- 3414 HODGKIN'S DISEASE MORTALITY AMONG PHYSICIANS. (E.) Vianna, N. J. (Cancer Control Bureau, New York State Dept. Health, Albany), M. D. Keogh, A. K. Polan and P. Greenwald. *Lancet* 7873:131-133, 1974.

All teaching hospitals in upstate New York were surveyed to identify New York physicians dying between 1960 and 1972 with histologically confirmed Hodgkin's disease. Thirteen male physicians were found to have died of Hodgkin's disease during the 13-yr period; this represents a death rate of 6.90/100,000 male population per year. The death rate from Hodgkin's disease for New York state during this period was 3.83/100,000 males aged 25 yr and over per year. The difference between the two rates is statistically significant, the relative risk for physicians being 1.8. The death rate from Hodgkin's disease in four counties with high economic status was also significantly lower than among the physicians. Only one dentist died from Hodgkin's disease during the study period, the death rate among dentists thus also being significantly lower than among physicians. Counties with the greatest number of registered physicians accounted for the greatest number of physicians' deaths from Hodgkin's disease. Deaths were distributed among various specialties with no one predominating. The higher death rate from Hodgkin's disease among physicians was probably related to the frequency and closeness of contact between physicians and Hodgkin's disease patients. Confirming studies among medical and paramedical personnel are needed.

- 3415 THE ROLE OF STARCHES IN THE ETIOLOGY OF GASTRIC CANCER. (E.) Modan, B. (Tel Aviv U. Med. School, Israel), F. Lubin, V. Barell, R. A. Greenberg, M. Modan and S. Graham. *Cancer* 34(6):2087-2092, 1974.

A dietary study of gastric cancer patients and matched control groups revealed a higher consumption frequency of starches among gastric cancer patients. Three control groups selected were: newly diagnosed cases of colorectal cancer; surgical cases with neither malignancy nor gastrointestinal disorders; and neighborhood controls. Subjects were matched to the gastric cancer cases by age, sex, ethnic origin, and length of residence in Israel, in order to protect against possible sources of bias. Data were analyzed both for individual food items and for selected groups of foods with common nutritional components. In comparing consumption frequency scores between cancer patients and controls, only items of "meaningful significance" were used. These had the criteria that: statistically significant differences were found between gastric cancer cases and two control groups, with differences from the third control group being at least of borderline significance and in the same direction; and, the differences between the control groups themselves were not significant. Of all food groups and sub-groups compared, only starches showed differences of "meaningful significance" between cases and controls. The higher frequency of starch consumption for gastric cancer patients was true for all ethnic groups and all socioeconomic strata. One explanation for the association between long-term starch consumption and gastric acid secretion and thus render the gastric mucosa susceptible to an exogenous carcinoma. It is also suggested that a higher consumption frequency of starches is associated with general overeating and, similarly, a higher cancer risk.

- 3416 HODGKIN'S DISEASE IN SCHOOLTEACHERS (CONT.). (E.) Hoover, R. (Natl. Cancer Inst., Bethesda, Md.). *N Engl J Med* 291(9):473, 1974.

Evidence that Hodgkin's disease occurs excessively in schoolteachers was challenged on the basis that the method of analysis (proportional mortality) might be subject to bias, especially since teachers appear to be at less risk of mortality from all causes. The population of male teachers at risk in Washington state was derived from the 1950, 1960, and 1970 censuses of the population. Average annual age-specific mortality rates from all causes and from Hodgkin's disease among all males in the state (from 1960-1969) were applied to these population estimates to derive data on the observed and expected deaths from all causes and from Hodgkin's disease among the state's male schoolteachers. A relative deficiency of deaths from all causes (relative risk, 0.7) and a slight relative excess of deaths from Hodgkin's disease (relative risk, 1.5) were found. Thus, the transmission of Hodgkin's disease between teachers and students is not a major epidemiologic feature of this disease.

3417 FEATURES OF LARYNGEAL CANCER DISTRIBUTION
IN DIFFERENT REGIONS OF THE UKRAINIAN SSR.

(*Rus.*) Tsiganov, A. I. (Kiev Sci. Res. Inst. Otolaryngol., USSR) and V. N. Samokhodskii. *Vopr Onkol* 20(12):13-18, 1974.

Studies were made of 2296 cases of laryngeal cancer observed in 19 regions of the Ukrainian SSR between 1965-1970. The highest incidence of cancer was found among the males living in the steppe area (6.94); the lowest, among males in the woodland area (2.90). Comparative studies showed that the incidence of laryngeal cancer was higher among rural males than urban males in the steppe area (7.35 and 5.56 resp.); in the woodland area the indices were 2.55 and 1.79 resp. No significant difference was observed in the incidence of cancer among the males and females of the areas in question. The highest incidence in the steppe area was found in the 50-59 age group (29.95); in the forest-and-steppe area and the woodland area, in the 60-69 age group (15.80 and 16.91 resp.). It is suggested that the higher agricultural and industrial development of the rural regions in the steppe area of the Ukraine may adversely affect the population by greater exposure to noxious effluents and polluted areas. It is also suggested that the so-called "factor of the South" (lower relative humidity, higher air temperature, and frequent dry winds) may contribute to a higher incidence of laryngeal cancer in the southern steppe areas.

3418 INCIDENCE OF LUNG CANCER IN THE AZERBAIDZHAN SSR. (*Rus.*) Saenko, Z. M. (G. M. Musabekov Republican Sci. Res. Inst. Virol. Microbiol. Hyg., USSR) and A. M. Lur'e. *Vopr Onkol* 20(2):87-88, 1974.

Study was made of the incidence of lung cancer correlated with the age and sex of patients in two mountainous areas of the Caucasus with different climatic conditions. The total average incidence of lung cancer in the region at a moderate altitude was 5.2 per 100,000, which was twice as high as the incidence in the other region located at a high altitude. The sex distribution was 100 females/300 males in the first area and 100/6,400 in the second. The highest incidence of the disease was among the males over 70 yr old in the first group and in the 60-69 yr male age group in the second. The data obtained show that climatic conditions play an active part in the origin and epidemiology of lung cancer in Azerbaidzhan.

3419 A RETROSPECTIVE STUDY OF LUNG CANCER IN BOMBAY. (*E.*) Notani, P. (Cancer Res. Inst., Tata Mem. Ctr., Bombay, India) and L. D. Sanghvi. *Br J Cancer* 29(6):477-482, 1974.

The epidemiology of lung cancer in India and its relation to smoking habits was investigated by means of a retrospective study of 520 lung cancer patients at a Bombay hospital from 1963 to 1970. Controls (patients diagnosed as not having cancer) were

matched from the hospital population for age, sex, and community. Of 413 smokers, only 56 smoked cigarettes; the majority smoked small bidis. The relative risk of lung cancer for bidi (2.64) and cigarette (2.23) smokers was almost the same and is significantly higher than for nonsmokers. There was also a preponderance of epidermoid and anaplastic types of carcinomata among smokers as against adenocarcinomata. A lower incidence of lung cancer among this Indian population than among Western populations may be attributed to a lower prevalence of the smoking habit in the population. Other suggested explanations for the lower relative risk for smokers in this group were mode of inhalation, differences in age of starting the habit, and environmental or genetic differences.

3420 THE EPIDEMIOLOGIC AND GENETIC ASPECTS OF AN OUTBREAK OF LEUKEMIA AMONG HAMADRYAS BABOONS OF THE SUKHUMI MONKEY COLONY. (*E.*) Lapin, B. A. (Inst. Exp. Pathol. Ther. USSR Acad. Med. Sci., Sukhumi). *Bibl Haematol* (39):263-268, 1973.

An outbreak of leukemia among a troop of hamadryas baboons of the Sukhumi Monkey Colony was investigated to determine genetic factors in the significant and rapid increase of incidence of the disease. Prior to 1967, no leukemia had been reported among hamadryas baboons. The disease appeared in animals which had been in contact with each other and with 10 baboons used in experiments on the study of the etiology of human leukemia since 1966. Between 1967 and 1971, 33 cases of leukemia were recorded; 26 monkeys died of the disease. The incidence increased from one case in 1967, to 5 in 1968, to 8 in 1969, to 11 in 1971, out of a troop of about 900 animals. All the monkeys who died were sexually mature aborigines, and were over five yr old. The troop has been highly inbred for 30 to 40 yr. Of 304 baboons imported to the colony, and not of this pedigree, none developed leukemia. Thus, the difference in mortality rates of leukemia in monkeys over five yr of age born in Sukhumi (6.4%) and in those imported from Africa (0.0%) is statistically significant.

3421 PHYSICAL AND DEMOGRAPHIC FEATURES OF MEN BEFORE DEVELOPING CANCER OF THE PROSTATE. (*E.*) Greenwald, P. (New York State Dept. Hlth., Cancer Control Bur., Albany), A. Damon, V. Kirmass and A. K. Polan. *J Natl Cancer Inst* 53(2):341-346, 1974.

Between 1880 and 1916, detailed physical and anthropometric measurements were performed on about 18,000 Harvard University students, of whom 2631 were also photographed between 1880 and 1912. Two hundred and sixty eight of these men later died of prostate cancer. The physical characteristics, marriage and fatherhood histories, and social and work-related activities were compared with those of 536 controls. The anthropometric indices of somatotype, gynandromorphy, androgyny, baldness, hair color, eye color,

and pilosity were similar for the prostate cancer cases and the controls, as were a number of other physical characteristics. There were no significant differences in age at death, proportion ever married, age at first marriage, age when first child was born, age when last child was born, occupation, or college or post-graduate activities between the two groups. Neither were there any significant differences in the ethnic socioeconomic, or occupational backgrounds of the fathers of the two groups. Of 197 married men with prostatic cancer, 29 had no children, compared with 49 of 228 married controls ($P = 0.06$). These data argue against the genetic factor being of much significance in the development of prostatic cancer within the population studied.

- 3422 FATAL RHABDOMYOSARCOMA AMONG CHILDREN IN THE UNITED STATES, 1960-69. (E.) Miller, R. W. (Epidem. Branch, Natl. Cancer Inst., Bethesda, Md.) and N. A. Dalager. *Cancer* 34(6):1897-1900, 1974.

A bimodal age distribution for deaths from rhabdomyosarcoma in United States children and adolescents has been discovered. The two peaks are related to anatomical site and were seen to occur one soon after birth and the other at 15 to 19 years. A sample size of 1170 was taken from death certificates over a ten year period. The early peak is attributed to mortality from tumors of the head, neck, and genitourinary system. The sex ratio (M/F) for rhabdomyosarcoma was highest for the genitourinary tract (2.0), lowest for the head and neck (1.2), and intermediary for the extremities and trunk (1.4). The rank order of fatal rhabdomyosarcoma by anatomical site for cases under 15 years of age was as follows: head and neck, 43.2%; genitourinary tract, 28.6%; trunk, 16.0%; limbs, 12.2%.

- 3423 FREQUENCY OF SKIN CANCER AND SOLAR KERATOSES IN A RURAL SOUTHERN COUNTY AS DETERMINED BY POPULATION SAMPLING. (E.) Zagula-Mally, Z. W. (U. Tennessee Coll. Med., Memphis), F. W. Rosenberg and M. Kashgarian. *Cancer* 34(2):345-349, 1974.

The frequency of skin cancer and solar keratoses in a rural Tennessee county was surveyed using techniques of cluster sampling. Trained nurses and dermatologists interviewed and examined 978 Caucasian adults, ages 21 and over during the period 1969-1971. Of these, 16.3% were found to have solar keratoses (usually multiple), and 4.4% appeared to have skin cancers. The prevalence of skin cancer increased sharply after the age of 65, indicating that the incidence of new disease was occurring rapidly after this age and points to a relationship of solar keratoses to skin cancer. The irregularity of female rates before age 70 may be an indication that women seek treatment earlier than men or spend less time outdoors. Medical treatment of solar keratoses with topical 5-fluorouracil offers a reasonable solution at a manageable cost while surgery is urged as a treatment for skin cancers.

- 3424 EPIDEMIOLOGY OF SELECTED SARCOMAS IN CHILDREN. (E.) Chabalko, J. J. (Mayo Grad. Sch. Med., Rochester, Minn.), E. T. Creagan and J. F. Fraumeni, Jr. *J Natl Cancer Inst* 53(3):675-679, 1974.

To complement a previous survey of childhood rhabdomyosarcoma, the epidemiologic features of other sarcomas with soft tissue predominance were studied. Data were obtained from 399 death certificates of U.S. children dying between 1960 and 1968 of soft tissue sarcomas, and hospital records of 297 additional children. Mortality was highest at ages 0-4 years and 15-19 years and was attributed mainly to fibrosarcoma and neurofibrosarcoma. The tumors primarily arose in the head and neck in younger children but predominated in the lower extremities in adolescents. There was no significant variation in annual mortality rates, season of birth, or geographic distribution among children developing these sarcomas. This shift may be related to the accelerated rate of soft-tissue growth in the limbs at the onset of puberty. Fibrosarcoma was the most common tumor at major sites, although liposarcoma predominated in the retroperitoneum and mediastinum, and leiomyosarcoma predominated in the gastrointestinal tract. Genetic determinants were suggested by 2 familial occurrences of sarcoma, an excess of brain and perhaps breast neoplasms in family members, and the relationship of certain cases to multiple neurofibromatosis (von Recklinghausen's disease).

- 3425 SMOKING AND BLADDER CANCER IN EGYPT. (E.) Makhyoun, N. A. (Dept. Urology, Francis Delafield Hosp., New York, N.Y.). *Br J Cancer* 30(6):577-581, 1974.

A case control study was carried out on 365 Egyptian males to investigate the possible role of cigarette smoking in the etiology of bladder cancer. A smoking index measuring the intensity and duration of smoking was calculated. Patients were divided into two groups, 278 (76%) with previous chronic vesical schistosomiasis (bilharziasis) and 87 (24%) without past infection. The smoking index was significantly higher for both bilharzial and non-bilharzial patients with bladder cancer than for their corresponding non-cancer controls. In non-bilharzial patients, a significant association was found between heavy and moderate smoking and bladder tumors; this confirms studies on patients in non-bilharzial countries. In bilharzial patients, however, the apparent association was not significant, due, possibly, to the younger age at which bilharzial subjects develop bladder cancer and to the lower income status of bilharzial subjects, who smoked fewer cigarettes. The local habit of water pipe smoking of "meassel" was not found to be significantly associated with bladder cancer. The results of the study support the view that cigarette smoking, particularly prolonged heavy smoking, is one of the factors in the etiology of bladder cancer.

- 3426 DOES SMOKING CAUSE CANCER? (E.) Burch, P. (Dept. Med. Physics, U. Leeds, England). *New Scientist* 61(886):458-463, 1974.

There is considerable evidence to indicate that lung cancer is not almost entirely due to cigarette smoking. Vertical data from cancer registries for sex-specific and age-specific onset and death rates in England, Wales, Finland, and Portugal between 1960-1962 show a sharper peak for older men than for older women. Values of S , the proportion of the population that appears to be "at risk" of lung cancer, often differ widely from country to country and from period to period, while the values of k_M and k_F (which are inversely related to the modal age), are generally similar from country to country and remained almost constant during the first half of the century. These data indicate that cigarette smoke is neither an initiator nor a promotor, while comparison of the time relation of the increases in cancer rates in the male population at risk with those of the female population at risk argues against the view that cigarette smoke is a precipitator of lung cancer. Necropsy studies argue against the possibility that the secular increases in cancer among the male and female populations were caused by an environmental, precipitating carcinogen unconnected with tobacco. Rather the increases appear to be largely or wholly spurious, resulting from changes in diagnostic accuracy and fashion. The data are best explained by the constitutional hypothesis, which holds that one or more of the genes which predispose to certain smoking habits are the same as or are associated with genes which predispose to various diseases. Other data show that the incidence of lung cancer among inhalers is significantly less than among noninhalers; that although the incidence of lung cancer among British doctors aged 35-64 yr who gave up smoking was lower than among those who continued smoking, lung cancer mortality was significantly elevated in the 65-84-yr age group, which had the lowest proportion of smokers and the highest proportion of ex-smokers; and the trends in the general male population in Britain resemble those among doctors.

- 3427 CANCER MORTALITY FOR MALES AND FEMALES AND ITS RELATION TO CIGARETTE SMOKING. (E.) Gentleman, J. F. (U. Waterloo, Canada) and W. F. Forbes. *J Gerontol* 29(3):518-533, 1974.

An investigation of whether trends in smoking habits across age and time can account for the observed changes in the ratio of male to female mortality rates is described. Male and female cancer mortality trends in five countries (South Africa, European population only; Canada; Chile; U.S.A.; and Israel, Jewish population only) across age and time are described. Graphic representations of the observed changes are included: specifically, plots of the cross-sectional age-specific estimated logarithm (\ln) force of mortality for males and females, plots showing time trends of male and female force of mortality at specific ages, and similar plots for the male/female mortality ratio. These are based on the

application of weighted regression techniques for fitting \ln force of mortality to polynomials in age. The plots show marked changes for major smoking-related cancers which are difficult to explain except on the basis of a substantial external effect. Changes in cigarette smoking habits appear to account satisfactorily for the observed changes.

- 3428 GEOGRAPHIC CORRELATIONS BETWEEN CANCER MORTALITY RATES AND ALCOHOL-TOBACCO CONSUMPTION IN THE UNITED STATES. (E.) Breslow, N. E. (Sch. Pub. Health, U. California, Los Angeles) and J. E. Enstrom. *J Natl Cancer Inst* 53(3):631-639, 1974.

Average annual age-adjusted cancer mortality rates for 1950-1967 were correlated with per-capita consumption of cigarettes, spirits, wine, and beer as estimated from tax receipts in 41 states of the United States in 1960. These correlations were made for cancers of 19 sites for white males and of 20 sites for white females. Multiple regression analyses were used to estimate the simultaneous effects on cancer mortality of state-to-state variation in the urban component of the population and in the consumption of spirits, beer, and cigarettes. Respiratory cancers were related to cigarette consumption, certain cancers of the upper alimentary tract to consumption of spirits, and cancers of the stomach, large bowel, kidney, bladder (for men), and breast (for women) to consumption of beer. The strongest single association was between rectal cancer and beer consumption, a result found also with similar data for 24 other countries. The hazards of attempting to draw sound scientific inferences from such data are acknowledged and must await confirmation and explanation by direct observation of the individual.

- 3429 ON THE FREQUENCY OF TUMOR INDUCTION IN A THOROTRAST KIDNEY. (E.) Verhaak, R. L. O. M. (Dept. Radiol., St. Ignatius Hosp., Breda, Netherlands) and A. E. Harmsen, A. J. M. van Unnik. *Cancer* 34(6):2061-2068, 1974.

Ten patients with Thorotrast kidney, who had submitted to retrograde Thorotrast pyelography in the early 1930's, were studied in order to acquire information about the frequency and types of lesions developing in such kidneys. Findings were made on the basis of nephrectomy and autopsy. A definite causal relation between the presence of Thorotrast below the pelvic mucosa and the development of epithelial abnormalities was indicated. No direct relationship was proved between amount of Thorotrast, latency, and development of malignancy. Out of the group of patients, 2 patients' nephrectomies indicated no epithelial abnormalities 24 to 25 years after pyelography, 5 patients developed malignant changes in the epithelium of the renal pelvis after a 21 to 35 year latent period, and 3 patients had kidneys with metaplastic and dysplastic epithelium 35, 35, and 37 years, resp., after the Thorotrast pyelography.

3430 OCCULT THYROID CARCINOMA IN OLMSTED COUNTY, MINNESOTA: PREVALENCE AT AUTOPSY COMPARED WITH THAT IN HIROSHIMA AND NAGASAKI, JAPAN. (E.) Sampson, R. J. (Dep. Surg. Pathol., Mayo Clin. Found., Rochester, Minn.), L. B. Woolner, R. C. Bahn and L. T. Kurland. *Cancer* 34(6):2072-2076, 1974.

Among 157 thyroid autopsies from Olmsted County, Minnesota, nine occult carcinomas of the thyroid were found, a prevalence of 5.7%. This rate is significantly lower than that reported from a previous autopsy series from Hiroshima-Nagasaki, Japan in which similar pathologic methods and diagnostic criteria were used. Sex ratio, age distribution, and radiation exposure were not considered to be explanations of this difference; the Japanese series had excluded patients who received direct atom bomb radiation. A true difference between the Japanese and American populations with respect to the prevalence of occult thyroid carcinoma is suggested. Factors related to this difference may be environmental (such as higher Japanese iodine intake or greater exposure to carcinogens through air and water pollution), or may be genetic and socio-cultural. While a high prevalence of occult thyroid carcinoma (13-24%) exists in Japan, low incidence rates and death rates from thyroid carcinoma are found. This is an indication that the factors causing a small occult tumor are dissociable from those causing clinically evident or death-causing thyroid carcinomata.

3431 CARCINOMA OF THE URINARY TRACT AND URINARY RETENTION IN UGANDA. (E.) Anthony, P. P. (Middlesex Hosp. Med. Sch., London, England). *Br J Urol* 46(2):201-208, 1974.

The incidence rate of carcinoma of the renal pelvis, bladder, and urethra in Uganda in the period 1964-1968 was 4.6/100,000 for males and 0.9/100,000 for females, the overall incidence, age, and sex distribution being similar for all three sites. The male:female ratio was 8.1:1, and the mean age was 54.8 yr. There was no evidence of schistosomal infection in any of the histological material examined, although both bladder and urethral carcinomas were associated with urethral strictures of gonococcal origin. The highest proportion of strictures was found in squamous cell carcinoma, followed by adenocarcinoma, the lowest proportion being found in transitional cell carcinoma. Patients with strictures averaged 6 years younger than those without. Squamous or glandular metaplasia and carcinoma *in situ* were present in a large proportion of cases, generally in association with strictures. Both squamous cell carcinoma and adenocarcinoma were more common in this sample than in the more temperate zones of the world, while transitional cell tumors were unusually rare in the Ugandan sample. Diet may be an important etiologic factor in urinary cancer in Uganda, both a dietary overload of tryptophan and increased beta-glucuronidase activity being potentially implicated. Urinary stasis probably enhances the development of urinary tract carcinoma and appears to be capable of modifying its histological type, probably through metaplasia.

3432 EPIDEMIOLOGIC STUDIES OF ENZOOTIC BOVINE LEUKOSIS ASSOCIATED WITH THE PUBLIC CONTROL PROGRAM IN DENMARK, 1959-1971. (E.) Bendixen, H. J. (Nat'l. Vet. Serum Lab., Copenhagen, Denmark). *Bibl Haematol* (39):215-219, 1973.

The etiologic nature and pathogenesis of enzootic bovine leukosis and the coherence between leukosis tumor cases and persistent lymphocytosis among Danish cattle has been investigated for over 20 yr. Results of public control measures for enzootic bovine leukosis in Denmark from 1959 to the present strongly support the hypothesis that persistent lymphocytosis and leukosis tumor cases are related. It was proposed and demonstrated that compulsory leukotic tumor case reporting, systematic hematologic examinations of animals in suspected herds, and slaughtering of herds with persistent lymphocytosis will eventually reduce the incidence of spontaneous tumor cases. This diagnostic control system was used in the high tumor incidence areas of Zealand, Lolland, and Falster, followed by slaughter of leukosis herds. Relative tumor incidence in this area dropped from 11.4 cases/10,000 head of cattle in 1968, to 11.3 in 1969, to 4.3 in 1970, to 3.0 six months later.

3433 CELL KINETICS AND GROWTH OF SQUAMOUS CELL CARCINOMAS IN MAN. (E.) Bresciani, F. (Inst. Gen. Pathol., U. Naples, Italy), R. Paoluzi, M. Benassi, C. Nervi, C. Casale and E. Ziparo. *Cancer Res* 34(9):2405-2415, 1974.

Five squamous cell carcinomas of the skin, lip, and gum were studied just before therapy and two were reinvestigated after treatment with methotrexate alone or combined with x-irradiation. The mean duration of DNA synthesis before therapy ranged from 18 to 34 hr, the mean intermitotic time ranged from 52 to 88 hr, the initial labeling index ranged from 11 to 36%, the growth fraction ranged from 31 to 84%, the cell birth rate ranged from 43 to 138 cells/hr and per 10^4 cells in the tissue, the cell loss rate ranged from 40 to 114 cells/hr and per 10^4 cells in the tissue, and the cell loss factor ranged from 78 to 93% of the cell birth rate. The distribution of intermitotic times was broad in most tumors, ranging from almost total symmetry to pronounced skewness. The intermitotic time distributions of recurrences after therapy may differ greatly from those of corresponding carcinomas before therapy. The doubling time appeared to correlate with the cell kinetic parameters of the tumors. The data suggest that a squamous cell carcinoma grows faster than normal tissue because of the cooperative effect of a higher cell birth rate and a smaller cell loss factor. The higher cell birth rate is largely the result of a larger growth fraction, with intermitotic time playing a marginal role. In particular, modal intermitotic times discernibly decrease with increasing growth rate. These correlations between cell kinetic parameters and the rate of tumor growth also apply to faster-growing recurrences as compared to corresponding tumors before treatment with either methotrexate or methotrexate plus x-radiation.

- 3434 A CYTOPHOTOMETRIC STUDY OF THE DNA DISTRIBUTION IN EHRlich ASCITES TUMOUR POPULATIONS AT DIFFERENT STAGES OF DEVELOPMENT. (E.) Andersson, G. K. A. (Inst. Zoophysiol., U. Lund, Sweden) and P. T. T. Kjellstrand. *Virchows Arch [Zellpathol]* 16(4):311-318, 1974.
- 3435 CANCER OF THE COLON AND RECTUM IN THE GERMAN DEMOCRATIC REPUBLIC. (Ger.) Berndt, H. (Central Inst. Cancer Res., Acad. Sci. East Germany, Berlin) and E. Varadi. *Arch Geschwulstforsch* 43(4):332-357, 1974.
- 3436 MAJOR SURVEY SHOWS DANGER OF WHITE BREAD. (E.) Anonymous. *New Scientist* 64(921): 316, 1974.
- 3437 INCIDENCE OF JAW TUMORS ON THE EAST COAST OF SOUTH INDIA. (E.) Reddy, C. R. R. M. (Andhra Med. Coll., Visakhapatnam, India). *Int Surg* 59(8):400-401, 1974.
- 3438 FAMILIAL MYELOMA. REPORT OF EIGHT FAMILIES AND A STUDY OF SERUM PROTEINS IN THEIR RELATIVES. (E.) Maldonado, J. E. (Mayo Clin. Fdn., Rochester, Minn.) and R. A. Kyle. *Am J Med* 57(6): 875-884, 1974.
- 3439 THE EPIDEMIOLOGY OF CANCER OF THE LARGE BOWEL. (E.) Wynder, E. L. (American Health Fdn., New York, N.Y.) and B. S. Reddy. *Am J Dig Dis* 19(10):937-946, 1974.
- 3440 ETHNICITY IS A SIGNIFICANT FACTOR IN THE EPIDEMIOLOGY OF RUBELLA AND HODGKIN'S DISEASE. (E.) Honeyman, M. C. (Roy. Alexandra Hosp. Children, Camperdown, Australia) and M. A. Menser. *Nature* 251(5474):441-442, 1974.
- 3441 COINCIDENCE OF PREGNANCY AND MALIGNANT NEOPLASMS. (Ger.) Pontuch, A. (Clin. Obstet. Gynecol., Komensky U., Bratislava, Czechoslovakia), E. Zajacova, O. Blaskova, A. Zilak, A. Bardosova, E. Somska and J. Chabada. *Arch Geschwulstforsch* 43(4):377-380, 1974.
- 3442 THE EPIDEMIOLOGIC PATHOLOGY OF CARCINOMAS OF THE LARGE BOWEL. (E.) Berg, J. W. (Natl. Cancer Inst., Bethesda, Md.) and J. D. Godwin II. *J Surg Oncol* 6(5):381-400, 1974.
- 3443 FAMILIAL OCCURRENCE OF TESTICULAR NEOPLASMS: A CASE REPORT. (E.) Gulley, R. M. (St. Francis Hosp., Peoria, Ill.), R. Kowalski and C. F. Neuheoff. *J Urol* 112(5):620-622, 1974.
- 3444 NEURAL NEOPLASMS IN THAILAND: A STUDY OF 2,897 CASES. (E.) Shuangshoti, S. (Fac. Med., Chulalongkorn U., Bangkok, Thailand) and R. Panyathanya. *Neurology* 24(12):1127-1134, 1974.
- 3445 MULTIPLE MYELOMA IN IOWA. (E.) Callis, M. N. (U. Iowa Coll. Med., Iowa City) and R. F. Sheets. *J Iowa Med Soc* 64(10):429-433, 1974.
- 3446 FAMILIAL POLYPOSIS AND PITUITARY CHROMOPHOBE ADENOMA. (E.) Metzger, P. P. (West Virginia Med. Ctr., Morgantown), A. S. Klainer, R. B. Gainer and W. M. Chaddock. *W Va Med J* 70(10):256-258, 1974.
- 3447 THE MODE OF GROWTH OF EXPERIMENTAL METASTASES IN RABBIT FEMORA. (E.) Faccini, J. M. (U. Coll. Hosp. Med. Sch., London, England). *Virchows Arch [Pathol Anat]* 364(3):249-263, 1974.
- 3448 A RESEARCH NOTE ON RECENT TRENDS AND DIFFERENTIALS IN CANCER MORTALITY IN TEXAS. (E.) Lee, E. S. (U. Texas, Sch. Pub. Hlth., Houston), R. E. Roberts and D. R. Labarthe. *Tex Rep Biol Med* 32(2):519-534, 1974.
- 3449 EPIDEMIOLOGY OF CANCER OF THE ENDOMETRIUM, THE OVARY AND ALL ORGANS OF THE FEMALE POPULATION IN HAMBURG 1956-1958 AND 1966-1968. (Ger.) Sachs, H. (U. Clin. Obstet. Gynecol., Hamburg/Eppendorf, Germany) and C. Hasche. *Z Krebsforsch* 81(2): 101-107, 1974.

See also:

- * (Rev): 3016, 3017, 3019, 3027
- * (Chem): 3042, 3054, 3101, 3138

- 3450 THE ETIOLOGY OF UTERINE CANCER. (Ger.) Schindler, A. E. (Univ. Clin. Gynecol., Tubingen, Germany) and F. Glaeser. *Geburtshilfe Frauenheilk* 34(3):186-194, 1974.

Clinical and hormonal risk factors were statistically evaluated in 142 patients with uterine cancer and in a control group of the same size. The average age at onset was 63.63 yr and the average age at menopause was 50.4 yr; both values are higher than those found in previous studies. Most patients with uterine cancer (23.2%) were between the ages 55 and 59 yr. Diabetes mellitus was found in 38% of the uterine cancer patients and in 15.3% of the controls. Hypertension was found in 57% of the cancer patients and in 32.3% of the controls. Symptoms of severe obesity were more frequent among uterine cancer patients than in the control group. The incidence of the estrogen effect in vaginal smears of the cancer group did not differ appreciably from that in the control group (51% and 47.1% resp.). Endometrial and vaginal atrophy were significantly more common in the controls (74.4 and 74.1%), only 25.8% of the controls showed evidence of endometrial proliferation in comparison to 47.2% of the cancer patients. Thus, the risk of developing uterine carcinoma is highest in subjects with obesity, diabetes mellitus, hypertension and with estrogen effect in the vaginal epithelium or endometrium after menopause.

- 3451 DIETARY PREFERENCE AND DISEASES OF AGE. (E.) Ross, M. H. (Inst. Cancer Res., Fox Chase Ctr., Philadelphia, Pa.) and G. Bras. *Nature* 250(5463):263-265, 1974.

Three complete isocaloric diets differing only in their casein and sucrose content were provided to Charles River COBS rats fed on the self-selection method from the age of 21 days until death, the oldest rat being 1,075 days. Control rats were fed each of the diets, one to a rat, *ad libitum*. Far more spontaneous tumors and cases of kidney, heart, and prostate gland disease occurred among the self-selection rats. The incidence of benign tumors without respect to type, adenomas and carcinomas without respect to site, leukemia, tumors of the anterior pituitary, adrenal, exocrine pancreas, and skin, among self-selection rats, surpassed that among all three conventionally fed groups combined. This was also true for advanced cases of glomerulonephrosis, myocardial fibrosis, and for prostatitis. More self-selective rats had multiple affections at time of death than those on fixed diets. Of the self-selection rats, 66% had at least 3 of these diseases as compared with 9, 26, and 28% for rats fed low, intermediate, and high protein diets, resp., at time of death. Once the diseases manifested themselves, the life span of self-selection rats was shorter than that of the other groups. Of those feeding on the conventional method, the frequencies of the non-neoplastic diseases and of several tumor types were dependent on the proportion of protein in the diet. Such protein dependencies were weak or nonexistent among self-selection rats. Self-selection rats grew more rapidly and attained higher body weights than controls. No two self-selection rats exhibited the same dietary preference.

Within the first 5 wk, most rats established the level of protein and carbohydrate that each would continue to select for a prolonged period. These results indicate that the dose-response interpretation of dietary habits cannot be applied to the free choice feeding situation. Rather, the increase in risk of developing tumors or other diseases of age is the direct consequence of the specific selections made by the individual in satisfying its unique metabolic needs.

- 3452 EXTRACELLULAR pH AND NEOPLASTIC TRANSFORMATIONS. (E.) Libenson, L. (Western Pennsylvania Hosp., Pittsburgh) and M. Jena. *Cancer Res* 34(5):953-957, 1974.

Cellulose bags containing acid or basic ion-exchange papers that yield various initial pH values when immersed in neutral 0.15 M NaCl were imbedded s.c. in several groups of rats. Also, bags containing neutral filter paper, empty cellulose bags, and single cellulose films were implanted in other groups of rats. All groups evolved tumors in diverse proportions and after latent periods of different length at the site of the implants. The bags containing basic papers that were neutralized *in vitro* to pH values near neutrality before implantation produced the highest incidence of tumors and exhibited the shortest latent periods of tumor formation. Most of the tumors examined histologically were fibrosarcomas composed of spindle cells with elongated cytoplasm and nuclei with tapered ends. The role of protracted low pH values in the environment of the cell and the possible existence of an optimum pH favorable for the neoplastic transformation are discussed.

- 3453 ESTROGENS IN WOMEN WITH PRIMARY LUNG CANCER. (Rus.) Zolotareva, T. M. (Saratov Med. Inst., USSR) and A. M. Lunts. *Vopr Onkol* 20(11):75, 1974.

The level of estrogens and 17-ketosteroids was measured in 64-hr urine specimens collected from 48 women, aged 41-81 yr, with primary lung cancer and in 30 healthy women. Of the 48 patients, 22 were studied before treatment and 26, after. The former showed a significant decrease in estradiol excretion and its percentage in the total estrogens; this was accompanied by an increase in estrone and estriol. After treatment a significant decrease occurred in estrone excretion and a slight increase in estradiol in patients given radiation therapy and surgery. It was observed that chemotherapy (unspecified) tended to decrease estrone excretion together with the percentage of estrone and estradiol, while increasing the percentage of estriol. Surgery was followed by a significant drop in the percentage of estrone. Urinary excretion of neutral 17-ketosteroids remained essentially normal. The total estrogen excretion in both groups of patients remained unchanged. Parallel studies of 73 men with lung cancer revealed a tendency for urinary excretion of estrone to be decreased and for estrone and estradiol to be increased before treatment.

- 3454 EVOLUTION AND SELECTIVE REDUCTION OF HORMONAL SECRETION IN THE MAMMOTROPIC PITUITARY TUMOR (MtT-F4). (E.) Molteni, A. (U. Kansas Med. Ctr., Kansas City), P. A. Nickerson and A. C. Brownie. *Virchows Arch [Zellpathol]* 16(3):271-279, 1974.

Severe hypertensive vascular disease was produced by implantation of the mammotropic tumor MtT-F4, secreting very large amounts of corticotropin, prolactin and growth hormone, in Fischer F344 female rats. The tumor has been maintained by continuous passage from rat to rat or stored frozen for three yr and then reimplanted. Implants with these new strains of tumor resulted in marked reduction or total loss of its hypertensiogenic ability. In addition to the failure to induce hypertension, the same strains of tumor also showed a reduced secretion of corticotropin. No alterations in the tumor secretion of growth hormone and prolactin were evident with the continuous passage from rat to rat. It is still uncertain whether a synergistic action of corticotropin, growth hormone, and prolactin is necessary to cause severe hypertensive vascular disease in the rats implanted with the mammotropic tumor. However, the present experiment indicates that among the three hormones secreted, corticotropin definitely plays a major role in the development of such disease.

- 3455 EFFECT OF AGE AND DURATION OF MENOPAUSE ON EXCRETION OF STEROID HORMONES IN BREAST CANCER AND PRECANCER. (Rus.) Bogdanova, A. G. (Sci. Res. Inst. Oncol. Radiol., Alma-Ata, USSR). *Vopr Onkol* 20(7):13-18, 1974.

Studies were carried out on the composition of 17-ketosteroids and the main metabolites of glucocorticoids in the urine of 69 healthy women, 35 with precancer of the breast and 65 with breast cancer from the early to the terminal stage. A correlation was established between the adrenal function in precancer and cancer patients and the age and the time of menopausal changes. A significant reduction of 17-ketosteroids was observed in cancer and precancer patients who were of reproductive age and in early menopause. In cancer patients who had not menstruated for over four yr, the 17-ketosteroid level did not differ significantly from that of the normal subjects. A significant increase in urinary cortisone and tetrahydro-cortisol derivatives was observed only in breast cancer patients who had not menstruated for over 10 years.

- 3456 THE RELATIONSHIP OF URINARY ANDROGEN METABOLITES TO BREAST DISEASES INCLUDING CARCINOMA. (E.) Wetchler, B. B. (Dept. Surg. Mt. Sinai Hosp., Elmhurst, N.Y.), J. McCarrick, J. Allerhand and D. Dreiling. *Mt Sinai J Med* 41(5):682-686, 1974.

A survey on the 24 hour urine samples of 163 women was conducted to determine if there is any correlation between the urinary excretion of androgen and corticosteroid metabolites and clinical status of patients with breast diseases. Women were divided

into four categories: normal controls, benign breast diseases, untreated breast cancer and mastectomized breast cancer. These were then subdivided into premenopausal and postmenopausal groups. No differences were found in the excretion of 17-ketosteroids and 17-hydroxycorticosteroids. There was a statistically significant decrease in urinary excretion of etiocholanolone in the treated and untreated postmenopausal breast cancer patients as compared to postmenopausal controls. No differences were seen in the premenopausal groups. The combined DHIA-androstosterone excretion was significantly less in the postmenopausal cancer patients than in the postmenopausal noncancer controls. The excretion of 11-desoxy-steroids was less in the postmenopausal controls. These differences could possibly be applied as a mass screening test for all postmenopausal females; positive urinary findings could indicate further evaluation for breast cancer.

- 3457 PROGENY OF CHILDHOOD-CANCER SURVIVORS. (E.) Li, F. P. (Natl. Cancer Inst., Bethesda, Md.) and N. Jaffe. *Lancet* (7882):707-709, 1974.

Inheritance of neoplasms in childhood and genetic effects of tumor therapy were examined in progeny of 46 childhood-cancer survivors, 17 males and 29 females. Among the 107 pregnancies recorded, there were 92 (86%) live births, 12 (11%) spontaneous abortions, and three (3%) induced abortions. Son/daughter ratio was 20/20 for male patients, and was 24/28 for female patients. Two neonatal deaths resulted from prematurity and 90 have survived. Birth defects in the live born included Hirschsprung's disease in one, and diverse lesser abnormalities in 13 others. The offspring have been free of cancer and other major chronic diseases. Under conditions of the study, no excess inherited defects were detected.

- 3458 CHROMOSOME STUDIES IN PLASMACYTOMA AND PLASMA CELL LEUKEMIA. (Ger.) Bauke, J. (Ctr. Internal Med. Pediatrics, U. Ulm, Germany), G. Kaiser and K. Schoffling. *Verh Dtsch Ges Inn Med* 78:122-125, 1972.

Chromosomal aberrations were studied in untreated patients with IgG-plasmacytoma, light-chain plasmacytoma, IgA-plasmacytoma, and in one case of plasma cell leukemia with IgD-paraproteinemia. The modal chromosome count was 46 in all cases, and the majority of the 839 metaphases investigated showed a normal diploid karyotype. Abnormal clones were not found in any of the 8 patients. Extrachromosomes occurred in sporadic hypodiploid, pseudodiploid, and hyperdiploid cells, preferably in groups C and G. A C-trisomy was found in 15 cells, and G-trisomy in 8 cells from different patients. Submetacentric extrachromosome of group A was found in two cells from one patient. The findings and data from the literature indicate the absence of any correlation between karyotype and paraprotein type or the clinical course of plasmacytoma. The aberrations observed are comparable with

(3459-3462)

those found in acute leukemias. Plasmacytoma is related to an instability of the genomes rather than to a specific chromosomal aberration. Malignant transformation may be released by one or more mutations, and aneuploidy may be regarded as a result of malignant transformation.

3459 CONGENITAL LEUKEMIA WITH CHROMOSOME ABERRATIONS (TRISOMY G) IN A NON-MONGOLOID INFANT.

(Ger.) Bjonness, H. (Pediatr. Clin., Cantonal Hosp., Aarau, Switzerland), E. M. Buhler, H. Fricker and E. Gugler. *Helv Paediatr Acta* 29(5):457-470, 1974.

Acute congenital myeloid leukemia is reported in a male newborn; the diagnosis was made on the first day of life. The pregnancy and delivery were normal, as were the hematological and chromosomal analyses in the parents. The somatically normal infant had pronounced hepatosplenomegaly. A WBC of 85,700/mm³ (81% paraleukoblasts, 1.5% neutrophils with rod-shaped nuclei and 11.5% neutrophils with segmented nuclei) was determined immediately after birth. Paraleukoblasts constituted 52.5% of cells in the bone marrow. Acute congenital myeloid leukemia was diagnosed. Cytogenetic studies revealed 47 chromosomes in 43 of 56 mitoses; 46 chromosomes in 10 mitoses and 45 chromosomes in 3 mitoses. Eight of 10 mitoses showed a G trisomy; these mitoses included all with 47 chromosomes and 4 of 5 with normal chromosome counts. The pseudodiploid karyotype of the remaining mitotic figure resulted from the loss of one chromosome belonging to group C or group F. A hypodiploid karyotype resulted from the absence of one group D chromosome. Trisomy G was a surprising finding since the patient had no clinical or radiological symptoms of Down's syndrome. Chromosome findings remained constant during cytostatic therapy until death at the age of 3.5 months. Chromosome analysis helps differentiate between leukemia and leukemoid reaction, while the number of chromosomes makes it possible to distinguish between myeloid and lymphoid leukemia.

3460 GIEMSA-BANDED CHROMOSOMES OF MOUSE MYELOMA IN RELATIONSHIP TO ONCOGENICITY. (E.)

Shepard, J. S. (Dartmouth Med. Sch., Hanover, N.H.), D. H. Wurster-Hill, O. S. Penttengill and G. D. Sorenson. *Cytogenet Cell Genet* 13(3):279-309, 1974.

G-banded karyotypes (413 in all) of the hypotetraploid mouse myeloma MOPC-21, five cell lines of the MOPC-315 tumor, and a cell line of the X5563 tumor were compared. Markers m 5 and m 8 were consistently present and may have derived from chromosomes 12 and 15 (or 18). In addition to these characteristic myeloma markers, one homolog of chromosome pairs 3, 12, and 15 and one of the Xs may have been altered or lost before tetraploidization occurred. One cell line which had spontaneously become nononcogenic with time in culture was studied before, during, and after this change. Associated karyotypic changes included: the addition of a large heterochromatic minute and a small marker, one half of which was centromeric heterochromatin; new rearrangements of chromosomes 3, 12 and X; and an apparent increase in the immunogenicity of the nononcogenic cell line.

3461 CYTOGENETIC INVESTIGATIONS IN CERVICAL PRECANCER. (Ger.) Dehnhard, F. (Munic. Hosp., Russelsheim, Germany). *Verh Dtsch Ges Pathol* 57:223-228, 1973.

Chromosome analysis was performed on epithelial tissue from the portion of 15 patients with carcinoma *in situ* and on another three with histologically confirmed cervical dysplasia. In 12 cases of carcinoma *in situ*, wide variations of the chromosome counts with frequency peaks either in the hypotriploid-hypertetraploid range or in the periploid range were found. Chromosomal aberrations were most pronounced in these cases. Marker chromosomes, a relative overrepresentation of group C chromosomes, and a relative underrepresentation of group D and G chromosomes were also observed in this group. The remaining six patients, who consisted of one with carcinoma *in situ*, three with dysplasia and two with carcinoma *in situ* and dysplastic regions, showed minor deviations in the chromosome count and an absence of marker chromosomes. The findings demonstrated a correlation or parallelism between the extent of chromosome abnormalities and the histological severity of epithelial atypia. This suggests the possibility of diagnosing cervical precancer by chromosome analysis. It is, however, presently impossible to determine the prognostic value of such differentiation.

3462 MOUSE TERATOCARCINOMA: CYTOGENETIC STUDIES OF PLURIPOTENTIAL CELLS. (Fr.) Guenet, J. L. (Inst. Past., Paris, France), H. Jakob, J. F. Nicolas and F. Jacob. *Ann Microbiol* 125(2):135-152, 1974.

Cytogenetic studies were made of 5 lines of undifferentiated cells derived from a single transplantable mouse teratocarcinoma. In 2 of the cell lines, the karyotype was normal, with 40 XY, and no rearrangement was discerned. One cell line had 40 chromosomes, including one Y in most cases and one reciprocal translocation. One cell line had a mode of 39 chromosomes with 2 isochromosomes, and no Y-chromosome could be identified. Finally, the oldest line had 41 chromosomes in most cells, with 1 isochromosome, no Y-chromosome, and several translocations. In general the cells are cytogenetically normal, as in the first two lines, and to some extent in the next two. This observation is an exception to the norm of finding severe karyotypic aberrations in such cultures. Furthermore, cells of the first 4 lines retained all their potentials, for they produced differentiated tumors when reinjected into mice, thus demonstrating a remarkable cytogenetic stability. Doubt is cast on one proposed mechanism for the formation of isochromosomes, which involves abnormal cleavage of the centromere, pericentric inversion, and cross-over; for these telocentric chromosomes, pericentric inversion seems improbable, and cross-over was observed to be very infrequent. It is noted that the same isochromosome occurred in each of two independently isolated cell lines.

- 3463 A STUDY OF A NEW HUMAN TUMOR CELL LINE (RHABDOMYOSARCOMA). (E.) Chapman, A. L. (Univ. Kansas Sch. Med., Kansas City,) P. Bogner and A. M. Behbehani. *Proc Soc Exp Biol Med* 146(4):1087-1092, 1974.

A primary culture was established from a tumor taken from the chest wall of an 80-year-old white female. The tumor was diagnosed as a probable embryonal rhabdomyosarcoma. The earlier cultures derived from it consisted of fibroblasts and occasional multinucleated giant cells. Between the 12th and 14th passages, the fibroblasts become progressively more rounded and fusiform; they tended to float free in clumps. Transfer of these cells alone resulted in a culture of attached round cells and multinucleated giant cells. The giant cells contained fibrils measuring 100 Å in diameter. The karyotypic pattern prior to, during, and after transformation showed a characteristic grouping around a modal number of 58. About 10% of the cells showed hyperploidy, and 85-95% showed a telocentric chromosomal marker. Cells maintained in continuous culture after treatment with 5-iododeoxyuridine, 20-methylcholanthrene, or DEAE-D showed no karyotypic changes compared with untreated cells. Electron microscopy revealed no virus particles in any culture examined. It is suggested that no "transformation" took place within the culture, the morphologic change which occurred being an adaptive cellular response to the *in vitro* conditions.

- 3464 POLYCYTHEMIA VERA: NEOPLASTIC TRANSFORMATION OF BONE MARROW CELLS *IN VITRO*. (Ger.) Kluge, N. (Max Planck Inst. Exp. Med., Göttingen, Germany), A. Knebel and H. Beckmann. *Verhandl Dtsch Ges Inn Med* 79:441-444, 1973.

Findings on the long-term culture of bone marrow cells obtained by sternal puncture of a 69-year-old untreated patient with polycythemia vera are presented. While the cytological findings in the third week were normal, 60% blasts, 38% lymphoid cells, and 2% orthochromatic erythroblasts were found following transformation of the cultured cells. After 22 weeks, 90% blasts, 8% orthochromatic erythroblasts, and 2% lymphoid cells were found. The chromosome number was 48 at all times. Synthesis of alpha- and beta-globin, and the occurrence of reverse transcriptase bound to particles with densities ranging from 1.16 to 1.19 g/cu cm, were detected in these cells. No interspecific antigen characteristic of C type virus was detected serologically. The particle-bound reverse transcriptase along with electron microscopic findings are indicative of the presence of an RNA tumor virus. The neoplastic transformations of the bone marrow cells were found to follow a program that had started in the cells prior to the *in vitro* cultivation. As shown by cytochemical and biochemical investigations, the cells belong in the erythrocyte compartment.

- 3465 STUDIES ON A CELL LINE DERIVED FROM THE L1210 MURINE LEUKEMIA WITH ALTERED SURFACE PROPERTIES AND DECREASED CAPACITY FOR TUMOR PRODUCTION. (E.) Kessel, D. (Grace Hosp., Detroit, Mich.) and H. B. Bosmann. *Cancer Res* 34(3):603-608, 1974.

A cell line (L1210/A) derived from the murine leukemia L1210 differed from L1210 in the following respects: (a) L1210/A adhered strongly to glass or plastic surfaces, and L1210 grows in suspension culture. (b) L1210/A produced a slow-growing tumor in BALB/c x DBA/2F₁ mice. Inoculation of 10⁶ cells killed these mice in about 21 days, in contrast to the 7-day survival with L1210; (c) L1210/A demonstrated a lower electrophoretic mobility than L1210; (d) incorporation of precursors into nucleic acid, protein, and glycoprotein was much slower in L1210/A; (e) L1210/A cells contain considerably less surface glycoprotein in papain-sensitive linkages; (f) level of a transferase involved in addition of sialic acid to a suitable receptor was lower in L1210/A, as were levels of several glycosidases. When grown in spinner culture, L1210/A cells respond by elevation of levels of enzymes involved in glycoprotein metabolism; electrophoretic mobility and enzyme levels return to values associated with L1210 cells. However, the tumor-producing ability of the spinner line is still below that of L1210, and the spinner culture cells will adhere to the vessel if stirring is stopped. Growth of L1210/A cells in spinner culture does not, therefore, produce a cell line equivalent to L1210.

- 3466 A NEUROBLASTOMA X GLIOMA HYBRID CELL LINE WITH MORPHINE RECEPTORS. (E.) Klee, W. A. (Lab. Gen. Comparative Biochem., Natl. Inst. Mental Health, Bethesda, M.) and M. Nirenberg. *Proc Natl Acad Sci USA* 71(9):3474-3477, 1974.

The specific binding of [³H] dihydromorphine was tested with mouse neuroblastoma (N18TG-2) and rat glioma (C6BU-1) cell lines, N18TG2 X C6BU-1 hybrids, various neuroblastoma lines, and neuroblastoma X L cell hybrids. Little or no specific binding of dihydromorphine was detected with N18TG-2 or C6BU-1, or with various other neuroblastoma cell lines. Specific narcotic receptors were found with one neuroblastoma X glioma hybrid (NG108-15), but relatively few specific narcotic binding sites were detected with a sister neuroblastoma X glioma hybrid line or with a neuroblastoma X L cell hybrid. With regard to the NG108-15 cells, only a portion of the binding of dihydromorphine was saturable. The specific binding sites discriminated between (+) and (-) enantiomers of the narcotics tested. There was only one class of dihydromorphine binding sites with a dissociation constant of 20-30 nM; the average cell contained approximately 3 x 10⁵ receptors. The relative binding strengths of the NG108-15 preparations for a series of narcotics were similar to those of a crude mitochondrial fraction of rat brain. The receptors appear to be localized on the plasma membrane.

- 3467 NATURE OF THE CELL CYCLE AND THE CONTROL OF CELL PROLIFERATION. (E.) Gilbert, D. A. (S. African Inst. Med. Res., Johannesburg). *Bio-systems* 5(4):197-206, 1974.

The concept that the dynamic state of the proliferating cell is dependent on a set of parameter values which determine the existence or nonexistence of oscillations in certain types of biochemical control systems and that the periodicity may be affected by suitably altering the magnitudes of any one or more of these parameters is discussed. This theory is further discussed in relation to: the wide variety of agents that can affect replication; the existence of distinct nonproliferative states; the continuous control of proliferation rate; variations in the sensitivity toward cell cycle inhibitory agents; senescence; and the "loss" of control of cell division in cancer.

- 3468 THE INTERACTION OF NORMAL AND TRANSFORMED CELLS IN PURE AND MIXED CULTURES. (Rus.) Pletiuskhina, O. Iu. (Lab. Math. Biol., Moscow State Univ., USSR). *Bull Eksp Biol Med* 77(10):91-94, 1974.

To study the sensitivity of cells to the inhibiting effect of population density, ³H-thymidine-labelled transformed fibroblast cells from the Syrian hamster and a cell line obtained by incubation of cytomegalovirus with Syrian hamster cells were inoculated into layers of homologous and heterologous cells. The transformed cells grew well in the presence of normal hamster fibroblasts and were inhibited in the presence of homologous cells, the density of the cell layers being equal. Thus, growth of transformed cells was related to the nature of the interacting cells, but not to their density.

- 3469 ABNORMAL DIFFERENTIATION OF LEUKEMIC CELLS *IN VITRO*. (E.) Morley, A. (Dept. Med., U. Adelaide, South Australia) and D. Higgs. *Cancer* 33(3):716-720, 1974.

Marrow or blood cells were obtained from 26 patients with acute myeloblastic leukemia (AML), two patients with AML supervening in chronic myeloid leukemia, one patient with AML supervening in polycythemia vera, three patients with acute myelomonocytic leukemia (AMML), and three patients with acute erythroleukemia (AEL). Morphological assessment of 28 cultures was possible after 9-12 days. In 4 of the 28 the cells which developed were indistinguishable from normal granulocytes, but in the remaining 24 the leukemic blasts developed into qualitatively abnormal cells showing a variable amount of somewhat disorganized differentiation. There was no discernible relationship between the type of leukemia and the subsequent appearance of the cultures. These results are in disagreement with recent reports that leukemic cells differentiate *in vitro* into normal cells. The fact that the leukemic myeloblasts in the present study differentiated into quantitatively and qualitatively abnormal cells supports the clonal theory of the nature of leukemia.

- 3470 FEATURES OF CELL PROLIFERATION IN REGENERATING RAT LIVER. (Rus.) Beliaeva, I. D. (Inst. Biol. Med. Chem., Moscow, USSR). *Tsitologia* 15(10):1297-1300

Studies were made of the dynamics of cell proliferation in regenerating rat liver after partial hepatectomy in random-bred 160-190 g albino rats. Data were obtained on the correlation between the mitotic activity and the daily periodicity at different stages of the regeneration, the relative number of primary and secondary cell divisions during the regeneration, and the features of the mitotic cycle of the cells dividing at different stages after the operation. The rats were sacrificed at 8 A.M. and 8 P.M., 28-96 hr after hepatectomy. Findings indicate that at the early stages of regeneration (24-48 hr after the operation) no daily periodicity of proliferation is observed (after 28 hr, during the highest mitotic activity) or it is insignificant (48 hr after the operation). At this stage, most of the mitoses occurred in the cells dividing for the first time. The cells dividing after 48 hr revealed a longer mitotic cycle including the S-period. At the later stages of regeneration (72-96 hr after the operation) the daily periodicity of cell division became more pronounced. Most of the mitoses during this stage were secondary cell divisions. This may explain the fact that the features of their mitotic cycle are similar to that of the cells dividing during the earlier stages of regeneration.

- 3471 DEFECTIVE DIFFERENTIATION OF MEGAKARYOCYTES IN ACUTE MYELOID LEUKEMIA. (E.) Brandt, L. (U. Hosp., Lund, Sweden), G. Levan, F. Mitelman and U. Sjogren. *Acta Med Scand* 196(3):227-230, 1974.

Bone marrow smears from a 78-yr-old woman with acute myeloid leukemia were examined for the percentage of megakaryocytes, and chromosome analyses were performed on bone marrow aspirate preparations. The bone marrow cells were very rich in cells with a myeloid:erythroid ratio of 3:1. There was a striking predominance of immature granulopoietic cells and 11.0% of the bone marrow cells were classified as myeloblasts. In addition, an accumulation of immature megakaryocytes (7.8%) was noted. Of the mitotic figures, 57.6% were found in granulopoietic precursor cells, 39.7% in erythroblasts, and 2.5% in megakaryocytes. Among 3000 metaphases, there were two octaploid and 21 tetraploid cells. All of 100 diploid cells had 46 chromosomes, and both of two tetraploid cells had 92. All of the diploid cells analyzed showed the same pseudodiploid karyotype: one chromosome 17 was replaced by one metacentric markers chromosome of C group size. The Giemsa banding pattern of all cells analyzed indicated that the metacentric marker was an isochromosome for the long arm of a chromosome 17. The two tetraploid cells showed the exact double pseudodiploid karyotype. The results indicate a defective differentiation of the megakaryocytes and/or their precursors analogous to what has been demonstrated in the myeloblasts of acute leukemia.

- 3472 DIFFERENCES IN MORPHOLOGY AND MITOTIC ACTIVITY BETWEEN INTRA- AND EXTRA-MEDULLARY ERYTHROPOIETIC TISSUE IN CHRONIC MYELOID LEUKEMIA. (E.) Sjogren, U. (Univ. Hosp., Lund, Sweden) and L. Brandt. *Scand J Haematol* 13(2):116-120, 1974.

The proportion, morphology, and mitotic activity of the basophilic erythroblasts within spleen and bone marrow smears from 20 untreated patients with chronic myeloid leukemia were studied. All of the patients had splenomegaly and none was in blast crisis. The spleen smears contained significantly more erythroblasts than the bone marrow preparations. Although the composition of the erythroblast series was similar in the two tissues, a significantly higher proportion of the spleen erythrocytes were megaloblastic compared with the marrow erythroblasts. Compared with the spleen erythroblasts, significantly more of the bone marrow erythroblasts were in mitosis; this discrepancy was most pronounced in the patients with moderate leucocytosis. In the patients with a very high white blood cell count at diagnosis, the difference in mitotic index was negligible. Extramedullary erythropoiesis may not be effective enough to compensate for the defective red cell production in the bone marrow.

- 3473 CHANGES IN ERYTHROPOIESIS IN ACUTE LEUKEMIA. (Ger.) Neumann, E. (First Med. Clin., Univ. Vienna, Austria) and N. Honetz. *Acta Med Austriaca* 1(1):13-16, 1974.

Serum vitamin B₁₂ levels were determined and cytochemical and erythrokinetic studies of erythropoiesis were performed on 27 patients with acute leukemia, including one patient with erythroblastosis. Serum vitamin B₁₂ levels ranged from 180 to 2,500 pg/ml in 10 patients with acute myeloblastosis, compared to a control range of 150-500 pg/ml. No correlation was found between the vitamin B₁₂ level and the type of the leukemia. No period acid-Schiff (PAS) positive material was found in any of the 22 cases of myeloblastosis. However, 93% of the erythroblasts in the patient with erythroblastosis were PAS-positive. Nonspecific esterase activity was significantly increased especially in the erythroblastosis patient, and granules were found in a ring-shaped area around the nucleus. Sideroblast counts determined in sternal bone marrow from myeloblastosis and erythroblastosis patients were 42.2% and 67%, resp. The apparent ⁵¹Cr half-life of erythrocytes averaged 13 days. Hemolysis in the spleen was found in two cases. The plasma iron half-life ranged from 100-320 min, averaging 169.1 min, while the plasma iron turnover averaged 0.73 mg/day/100 ml whole blood, and iron incorporation in the erythrocytes averaged 23.2% after 10 days. A primary increase in the iron activity over the liver with little or no increase over the sacrum was observed. No ineffective erythropoiesis was found in any of these cases. A ⁵¹Cr erythrocyte half-life of 14 days, a plasma iron half-life of 100 min, a plasma iron turnover of 1.15 mg/day/100 ml whole blood and an iron incorporation rate of 42.5% were measured in the blood sample from the patient with erythroblastosis.

- 3474 TOPOLOGIC ASSESSMENT BY USE OF WHOLEMOUNTS OF MITOTIC ACTIVITY IN THE HAMSTER MAMMARY GLAND DURING THE ESTROUS CYCLE. (E.) Purnell, D. M. (M.S. Hershey Med. Ctr., Hershey, Pa.) and G. C. Sagers. *J Natl Cancer Inst* 53(3):825-828, 1974.

Stained wholemounts of inguinal mammary glands prepared from colchicine-treated LSH/SsLAK hamsters killed at different phases of the estrous cycle were used to determine the temporal and topologic distribution (ducts *versus* lobulo-alveolar structures) of mitoses in the mammary gland during the estrous cycle. Two periods, one early and one late in relation to ovulation, of increased mitotic activity in the mammary gland were identified. During the first half of the estrous cycle after ovulation, the total mitotic activity of the mammary gland progressively increased; mitoses localized in lobulo-alveolar structures constituted the major fraction of the total mitotic activity during this interval. During the second half of the estrous cycle, the total combined mitotic activity was approximately 1/2 maximum and, again, the major fraction of the total mitotic activity was accounted for by lobulo-alveolar mitoses. In comparison to the early period, duct mitoses contributed less to the total mitotic activity in the second period.

- 3475 POLYSACCHARIDE PRODUCTION BY CULTURED B-16 MOUSE MELANOMA CELLS. (E.) Satoh, C. (Milton S. Hershey Med. Cent., Pennsylvania State Univ.), J. Banks, P. Horst, J. W. Kreider and E. A. Davidson. *Biochemistry* 13(6):1233-1241, 1974.

The production of polysaccharides and glycoproteins by two clones of the B-16 mouse melanoma and a primary explant culture of syngeneic normal iris melanocytes was studied after exposure of the cultures to [³H] glucosamine and ³⁵SO₄²⁻. The products were fractionated by differential salt extraction and porous glass bead chromatography. Hyaluronic acid, the predominant product of the iris melanocyte, was not detected in the 0.4 M salt eluate of the melanotic B-16 clone and was present to less than 0.5% in the amelanotic line. A major radioactive component of this fraction was sialic acid, all of which appeared susceptible to the action of neuraminidase. The remainder of the activity was distributed between the amino sugars, with galactosamine predominant; the latter probably represents a low-sulfated chondroitin sulfate of molecular weight 13,000-15,000. This high molecular weight chondroitin was not detected in the iris cultures. The main component of the 0.8 M salt eluate fraction of the melanoma cells appeared to be a relatively high molecular weight polysaccharide containing only galactosamine as the amino sugar component. The second component of this fraction was a mixture of heparitin sulfate and a small amount of a chondroitinase-susceptible component, apparently an under-sulfated chondroitin sulfate. The major component of both the 1.2 and 2.0 M salt eluate fractions appeared to be the more fully sulfated analog of the high molecular weight chondroitin. The iris fraction contained less than 1% of this high molecular weight material. The polysaccharides and

glycoproteins made by the melanotic and amelanotic B-16 clones appeared essentially identical, although they differed in relative amounts.

- 3476 STUDIES ON THE PROTEINS OF CYTOPLASMIC-MICROSOMAL FRACTION OF GUERIN TUMOUR DURING ITS GROWTH IN RATS. (E.) Farbiszewski, R. (Med. Sch., Bialystok, Poland) and W. Rzeczycki. *Neoplasma* 21(3):363-367, 1974.

The proteins of the cytoplasmic-microsomal fraction of Guerin tumors were separated chromatographically and by CM-Sephadex 10, 20, 30 days after transplantation of tumor cells into male Wistar rats. The proteins were analyzed by electrophoresis on a polyacrylamide gel. The tumor yielded four protein peaks. Peak III diminished during the last stage of tumor growth, while peak IV concomitantly increased. The amount of arginine in peak IV was about 3-fold higher than in the proteins of peaks I, II, III; the nitrogen concentration was also higher in the peak IV protein. The peak IV protein was basic in nature. The data suggest an enhanced biosynthesis of arginine-rich basic proteins in the cytoplasmic-microsomal fraction of Guerin tumor cells during growth.

- 3477 ISOLATION AND CHEMICAL CHARACTERIZATION OF MUCOPOLYSACCHARIDES FROM RAT TUMORS. (E.) Kuroda, J. (Dept. Chem., Ochanomizu U., Tokyo, Japan), S. Saito, N. Seno, S. Nagase and K. Anno. *Cancer Res* 34(2):308-312, 1974.

Mucopolysaccharides were extracted by Pronase digestion from two types of rat tumor tissues: MC sarcoma induced in Donryu rats by a single s.c. injection of methylcholanthrene (0.1 mg) and a solid tumor developed by s.c. transplantation of AH-109A cells into the animals. The mucopolysaccharides were fractionated by anion-exchange chromatography and characterized by chemical analysis, electrophoresis, infrared spectroscopy, and enzymic digestion. The mucopolysaccharides in the MC sarcoma were mainly hyaluronic acid and chondroitin sulfate A with small amounts of heparan sulfate and dermatan sulfate. In the solid AH-109A tumor, heparan sulfate was the major mucopolysaccharide, with hyaluronic acid, dermatan sulfate, and a trace of chondroitin sulfate A. This is the first isolation of heparan sulfate from solid tumors.

- 3478 CHOLESTEROL AS A BIOREGULATOR IN THE DEVELOPMENT AND INHIBITION OF LEUKEMIA. (E.) Inbar, M. (Lab. Membranes Bioregulation, Weizmann Inst. Sci., Rehovot, Israel) and M. Shinitzky. *Proc Natl Acad Sci USA* 71(10):4229-4231, 1974.

Leukemia in mice and humans is accompanied by a marked deficiency of unesterified cholesterol in the surface membrane of leukemic cells as compared with normal leukocytes. This deficiency induces a significant reduction in their membrane microviscosity.

Since cholesterol in the cell surface membrane is exchangeable with cholesterol in the serum lipoproteins, concomitant to the cellular cholesterol deficiency, the average level of cholesterol in the blood serum of leukemic patients is substantially below the average normal level. These facts strongly suggest that the cholesterol level in the cell surface membrane lipid core and in the blood serum can be utilized to regulate processes which are associated with the development of leukemia. It is hypothesized that when the ratio of cellular cholesterol to phospholipids and the level of unesterified cholesterol in the serum are below normal ranges, the rate of cholesterol accumulation in the cell surface membrane can decrease to a critical level where the membrane microviscosity will retain a reduced value characteristic of leukemia cells. The reduced levels of membrane cholesterol and microviscosity could, therefore, result either from genetic defects in the rates of cellular biosynthesis of cholesterol and phospholipids during the development and maturation of normal leukocytes or from metabolic defects in the sources that supply unesterified cholesterol to the lymph and the blood stream. Thus, a controlled reduction of the cholesterol level in normal leukocytes might sensitize immune response processes or phagocytic activity above the threshold level beyond which malignant transformation and the development of leukemia might occur. Or, a controlled enrichment of the cellular cholesterol in leukemic cells might prevent the development of latent leukemia and might remit leukemia in its active form.

- 3479 TRYPTOPHAN METABOLISM AND CORTICOSTEROIDS IN BREAST CANCER. (E.) Fahl, W. E. (Univ. Wisconsin Med. Sch., Madison), D. P. Rose, L. Liskowski and R. R. Brown. *Cancer* 34(5):1691-1695, 1974.

Plasma cortisol levels and the urinary excretion of tryptophan metabolites, free cortisol, and corticosteroid sulfates were studied in five patients with State I or II breast cancer, six patients with locally recurrent disease, and 19 breast cancer patients with multiple metastases to various sites. Twelve of the 30 patients had abnormal tryptophan metabolism in that they excreted all five metabolites of tryptophan (kynurenine, hydroxykynurenine, acetylkynurenine, xanthurenic acid, and kynurenic acid) in significantly greater quantities than did healthy controls. As a group, the patients with abnormal tryptophan metabolism also excreted significantly higher levels of both urinary free cortisol and corticosteroid sulfates than the patients with normal tryptophan metabolism; however, there was considerable overlap, and some patients with grossly elevated tryptophan metabolites did not differ in corticoid excretion from the patients with normal tryptophan metabolism. Abnormal tryptophan metabolism was not associated with higher plasma cortisol levels. The patients with widespread metastases excreted higher levels of tryptophan metabolites than those with early breast cancer or locally recurrent disease, but the groups did not differ significantly in terms of urinary free cortisol excretion or plasma cortisol levels. Two metastatic cancer patients excreted greatly elevated amounts of urinary corticosteroid sulfate; when the values for these pa-

tients were excluded, there was no correlation between tryptophan metabolite and corticosteroid sulfate levels. Increased adrenocorticosteroid secretion due to stress does not appear to be a major factor in produced abnormal tryptophan metabolism in breast cancer.

3480 INCORPORATION OF ARGININE BY SOLUBLE EXTRACTS OF ASCITES TUMOR CELLS AND REGENERATING RAT LIVER. (E.) Tanaka, Y. (Fox Chase Ctr. Cancer Med. Sci., Philadelphia, Pa.) and H. Kaji. *Cancer Res* 34(9):2204-2208, 1974.

Soluble amino acid incorporation systems from ascites tumor cells, regenerating and regenerated rat liver, and normal rat liver were tested for incorporation of 12 radioactive amino acids. Arginine showed the greatest incorporation by the ascites tumor soluble system. The system was dependent on an energy source (ATP and ATP-generating system) and tRNA from ascites tumor or *E. coli*. Puromycin inhibited the incorporation by 50% and RNase inhibited it completely. No requirement for guanosine-5'-triphosphate or an amino acid mixture was observed. The amount of incorporation increased as the amount of arginyl-tRNA-¹⁴C increased. The activity of the soluble system from the regenerating rat livers increased as a function of time after partial hepatectomy, the soluble system from the regenerated liver (3 or more days after surgery) being twice as active as the system from normal liver. The soluble system from ascites tumor cells was 5-10 times more active for aminoacyl-tRNA synthesis for arginine than the system from regenerated liver. Once the amino acid is incorporated into the free amino group of an acceptor protein, it is probably not exchanged with the amino acid of aminoacyl-tRNA. The soluble system may be involved in a growth-regulatory mechanism.

3481 DIFFERENT DEGRADATION RATES OF ALKYLATED RNA, PROTEIN AND LIPIDS IN NORMAL AND TUMOR CELLS. (E.) Lerman, M. I. (Inst. Biol. Med. Chem., Acad. Med. Sci., Moscow, USSR), O. Yu. Abakumova, N. G. Kucenco, L. B. Gorbacheva, G. V. Kukushkina and A. M. Serebryanyi. *Cancer Res* 34(7):1536-1541, 1974.

Hepatosarcoma 22a was transplanted s.c. into adult C3HA mice, which were injected 12 days later with *N*-methyl-*N*-nitrosourea-1-¹⁴C (MNU) (80 mg/kg, i.p.). The animals were killed 1, 5, 19, or 48 hr after MNU treatment. The radioactivity detected in the DNA, RNA, proteins, and lipids 1 and 5 hr after MNU administration was retained for at least 48 hr in the hepatoma cells, but was rapidly eliminated from the liver and spleen. These results imply the presence of fundamental differences in macromolecular metabolism of these cell types. Moreover, the differences observed are probably not only between rapidly and slowly proliferating cells but also between normal and tumorous cells. The data suggest that in dividing cells, the turnover rate of RNA, protein, and lipids, as well as of subcellular structures (ribosomes,

membranes), is decreased as compared with nondividing cells and is inversely related to the proliferation rate. It is also possible, although less probable, that hepatoma cells contain limiting concentrations of the enzymes responsible for the degradation of labeled molecules, and that these enzymes are more rapidly inactivated by MNU than they are in liver cells.

3482 METABOLISM OF NUCLEIC ACIDS IN HEPATOMA 46 AND NORMAL LIVER. (Rus.) Bogdanov, G. N. (Inst. Chem. Physics, Chernogolovka, USSR) and V. M. Shmonina. *Ukr Biokhim Zh* 46(2):181-187, 1974.

The synthesis and metabolism of nucleic acids in hepatoma 46 and normal liver were studied in male and female C3HA mice injected s.c. with 0.3 ml of tumor homogenate in physiological saline (1:1). When the tumor was growing fastest, the animals were sacrificed and the tumor was removed and frozen in dry ice. Nucleic acids were extracted with phenol. There was no significant difference between the total DNA and RNA content in hepatoma 46 and the normal liver. The rate of ¹⁴C-thymidine incorporation into DNA was higher in tumor tissue than in normal liver tissue. The rate at which RNA was metabolized in hepatoma 46 was somewhat faster than normal. DNA metabolism was substantially slower, which may be explained by the change of DNA activity, as well as by nuclease-resistant DNA-RNA-protein complexes found both in the liver and the hepatoma.

3483 ISOENZYMES OF GLUCOSE-6-PHOSPHATE DEHYDROGENASE IN MOUSE LIVER AND HEPATOMAS. (Rus.) Birk, R. V. (Inst. Exp. Clin. Med., Tallin, USSR). *Vopr Med Khim* 20(3):298-302, 1974.

Isoenzymes of glucose-6-phosphate dehydrogenase (G-6-PDH) were studied in mouse liver and in primary and transplanted murine hepatomas and hepatoma 22a in adult male C3HA mice. Primary murine hepatomas were induced by giving mice 2.5 mg/kg/day diethylnitrosamine in their drinking water; hepatoma 22a was originally induced by giving mice a benzene solution of *o*-aminoazotoluene. Polyacrylamide-gel disk electrophoresis revealed four G-6-PDH isoenzymes with widely different activities in the liver and hepatomas. The total activity of G-6-PDH in hepatomas was four to five times greater than in the liver. The mobilities of isoenzymes I, II and III were found to be 10-25, 5-6 and 2-3 times faster, resp. than in normal liver. In the normal liver isoenzymes I, II and III account for 5.5%, 32.5% and 56.9%, resp. of the total activity. In primary hepatomas and transplants, the activity of isoenzyme I accounts for 21.7% and 20%-30%, resp. of the total G-6-PDH activity.

- 3484 ELECTRON HISTOCHEMICAL AND BIOCHEMICAL STUDIES OF GLUCOSE-6-PHOSPHATASE AND β -GLYCEROPHOSPHATASE ACTIVITIES OF THE CELL NUCLEI IN NORMAL RAT LIVER AND HEPATOMA 27. (Rus.) Bukhvalov, I. B. (Inst. Exp. Clin. Oncol., Moscow, USSR), Ia. M. Cohen, A. G. Perevoschikov and N. T. Raikhlin. *Biull Eksp Biol Med* 78(12):99-102, 1974.

Glucose-6-phosphatase activity in the cell nuclei of normal rat liver and hepatoma-27 was localized mainly in the perinuclear space. The activity of this enzyme was significantly lower ($1.2 \pm 0.08 \mu\text{M}/\text{min/g}$ protein) in the nuclei of hepatoma-27 than in normal rat liver ($37 \pm 0.45 \mu\text{M}/\text{min/g}$ protein). Histochemically a little β -glycerophosphatase activity was observed in rat liver nuclei incubated at pH 6.4; none was detected in nuclei of hepatoma 27. Biochemical studies showed traces of β -glycerophosphatase in the nuclei of normal rat liver and hepatoma-27.

- 3485 COMPARATIVE ELECTRON CYTOCHEMICAL STUDIES OF LOCALIZATION OF SUCCINATE DEHYDROGENASE IN MITOCHONDRIA OF NORMAL, HYPERPLASTIC AND CANCER CELLS OF THE RAT THYROID. (Rus.) Dmitrieva, N. P. (Inst. Development Biol., USSR Acad. Sci., Moscow) and E. A. Amirkhanian. *Tsitologiya* 15(2):156-160, 1973.

A comparative cytochemical submicroscopic study was made of succinate dehydrogenase (SDG) distribution in the mitochondria of hyperplastic and tumor cells. Mitochondria of normal homologous tissue served as the controls. Normal and hyperplastic thyroid glands and thyroid gland tumors (strain TT-3) injected s.c. were taken from random-bred 220-260 g female albino rats. Cellular hyperplasia of the thyroid glands was induced by 6-methylthiouracil given in water. The total of four series was run with 160 specimens examined under the electron microscope. Findings indicate that mitochondria of cancer cells have a markedly lower succinate dehydrogenase activity compared with that of normal and hyperplastic cells. The final reaction product, copper ferricyanide, was observed in the form of rare small opaque granules located on the cristae within the intracrystal space and between the outer and inner membranes of mitochondria in cancer cells. It may be assumed that decreased activity of oxidative enzymes in the cancer cells is the result of certain structural features of cancer mitochondria.

- 3486 LACTATE DEHYDROGENASE IN NEUROBLASTOMA CLONES. (E.) Tholey, G. (Life, Earth Sci. Res. Unit, Louis Pasteur Univ., Strasbourg, France), B. Wurtz, J. Ciesielski-Treska and P. Mandel. *J Neurochem* 23(5):1083-1084, 1974.

The lactate dehydrogenase (LDH) activity was measured in dispersed cells and primary cultures of three neuroblastoma clones without neurotransmitter activity (N18, N9, S20), a cholinergic neuroblastoma clone (S21), and two adrenergic neuroblastoma clones (N115

and M1). Except for clones N18 and N115, the total LDH activity per mg protein was always higher in the cultured cells than in the fresh tumor cells. No correlation was observed between the doubling time of the different clonal lines (around 24 hr) and LDH activity. There was no apparent correlation between neurotransmitter metabolism and LDH activity. The differences in LDH activity were probably due to inherent metabolic differences. Five isoenzymes of LDH were separated by electrophoresis of a mouse brain extract. One of these isoenzymes, a muscle type LDH, was the only band present in the tumor cells, primary cultures, and several clones, except M1. In the latter clone, two other bands were present. The data suggest that, with respect to LDH activity, two types of neuroblastoma cells exist: embryonic-like cells (tumoral type), and more differentiated cells.

- 3487 ACTIVITY OF HYDROLYTIC ENZYMES IN THE CELLULAR STROMA OF MAMMARY GLANDS IN MASTOPATHIES AND CANCER. (Ger.) Knezevic, M. (Stomatol. Hosp. Zagreb, Yugoslavia), S. Knezevic-Krivak and B. Rode. *Verh Dtsch Ges Pathol* 58:506, 1974.

Histochemical studies were performed on 49 patients with breast cancer and 26 with mastopathies. The large numbers of macrophages around and within cancer cell aggregates in invasive cancer had a very strong lysosomal reaction to acid phosphatase, and a weaker reaction to β -glucuronidase, nonspecific esterase and N-acetyl- β -glucosaminidase. The proliferation of such macrophages may be related to the activity of the cancer cells. Many cancer cells showed evidence of damage and necrosis and were destroyed by phagocytosis. Most stromal mast cells had a negative reaction to acid phosphatase, a weak positive reaction to β -glucosaminidase, a moderately strong reaction to nonspecific esterase and a strong positive reaction to β -glucuronidase. The cancer cells were often surrounded by mast cells, both in the mammary gland and in lymph node metastases. The proliferation of mast cells may be related to infiltrative cancer growth.

- 3488 THE SYNTHESIS OF RAT LIVER CATALASE DURING TUMOR GROWTH. (Rus.) Komov, V. P. (Inst. Pharm. Chem., Leningrad, USSR) and T. F. Rakhmanina. *Vopr Onkol* 20(11):48-50, 1974.

The rate constants of catalase synthesis were measured in rat liver during tumor growth with 3-amino-1,2,4-triazole (AT). Lymphosarcoma was transplanted into male rats. AT (1 g/kg) was injected i.p. 2, 7, 14 and 18 days after tumor transplantation. Catalase activity was measured 24 and 48 hr after the injection of the inhibitor. Within 24 hr after tumor transplantation, catalase synthesis decreased to less than one-tenth of its original value and was totally inhibited seven days later. It is suggested that tumor growth disrupts catalase synthesis at the transcription stage due to a decrease of synthesis-activating factor or to an increase in an inhibiting factor.

- 3489 A COMPARISON OF THE PHOSPHOFRUCTOKINASE ISOENZYME PROFILES OF TRANSPLANTABLE HEPATOMAS AND NORMAL LIVER. (E.) Kirby, W. (Dep. Biochem., Univ. Sheffield, England), H. P. Morris and C. B. Taylor. *Eur J Cancer* 10(9):629-631, 1974.

The phosphofructokinase (PFK) profiles of normal liver and transplantable hepatomas were studied. The hepatoma material consisted of samples of Morris hepatomas 9618A (highly differentiated), 16 (well differentiated), and 7777 (poorly differentiated). The total PFK activity was similar in liver and tumor 9618A, increasing progressively with decreasing differentiation in the other tumors. Thus, PFK activity appears to increase with growth rate. The isoenzyme patterns of all tumors were within the range of the isoenzyme types found in normal liver, and there was no obvious correlation between changes in the isoenzyme pattern and the degree of differentiation. No muscle-type enzymes were produced by the tumors. The results indicate that there was no production of new forms of PFK by the tumors studied.

- 3490 HUMAN LEUKEMIC CELLS: RNA-DIRECTED DNA POLYMERASE. (E.) Desai, L. S. (Children's Cancer Res. Found., Boston, Mass.), D. L. Short, O. M. Friedman and G. E. Foley. *Eur J Biochem* 47(3):453-460, 1974.

RNA-dependent DNA polymerase (reverse transcriptase) was isolated from human lymphocyte cell lines derived from patients with leukemia or infectious mononucleosis and from normal healthy donors. The enzyme was purified using high-speed glycerol gradients and DEAE-cellulose and phosphocellulose column chromatography. The cytoplasmic cell fractions exhibited greater endogenous DNA polymerase activity than did the nuclear cell fractions. The enzyme had a preference for divalent Mg^{2+} over Mn^{2+} and required all four deoxyribonucleotide triphosphates to exhibit the characteristics of DNA polymerase activity. There was a general pattern of increased activity resulting from purification. The enzymes isolated from all cell types studied showed similar chromatographic elution patterns. The purified enzyme isolated from the normal human cells showed low activity. The enzyme derived from one mononucleosis cell line showed near-normal activity, while that from another mononucleosis line showed considerably higher activity. The activity exhibited by the enzyme from the leukemic cell lines was greater than those of the enzymes from the other lines. In general, the reverse transcriptase activity preferred oligo(dT)·poly(rA) over synthetic templates. Oligo(dG)·poly(rC) was not preferred as a template by the reverse transcriptase, but was a comparatively better template for the normal and mononucleosis cells. The highest ratio of oligo(dT)·poly(rA):oligo(dG)·poly(rC) was obtained with the leukemic cells. The presence or absence of reverse transcriptase in cultured human cells cannot be taken as evidence for or against the presence of an RNA tumor virus.

- 3491 ACTIVATION OF GUANYL CYCLASE AND INTRACELLULAR CYCLIC GMP BY FIBROBLAST GROWTH FACTOR. (E.) Rutland, P. S. (Salk Inst. Biol. Studies, San Diego, Calif.), D. Gospodarowicz and W. Seifert. *Nature* 250(5469):741-742, 773-774, 1974.

In the presence of hydrocortisone, physiological concentrations of fibroblast growth factor (FGF), purified from bovine pituitary glands, cause the same transient increase in intracellular cyclic guanosine monophosphate (GMP) concentrations of quiescent cultures as those caused by serum. When FGF was added to resting BALB/c3T3 cells maintained in the presence of serum, the concentrations of cyclic GMP rose after 10 to 20 min by a factor of 10- to 15-fold over the value in unstimulated cultures. Addition of increasing concentrations of FGF in the presence of hydrocortisone caused concomitant increases in both the cyclic GMP concentrations measured at 20 min and the eventual induction of DNA synthesis and cell division. Little or no alteration was observed in cyclic AMP concentrations. Furthermore, FGF specifically activated the membrane-bound guanyl cyclase, but not the adenylyl cyclase system. Guanyl cyclase activities in the particulate (membrane-containing) cell fraction and in the plasma membrane fraction of 3T3 fibroblasts were stimulated 3- and 6-fold, resp., by FGF. It is suggested that growth-initiating polypeptide hormones interact with a guanyl cyclase system bound to the plasma membrane, in a way similar to that of the interaction between polypeptide hormones and the adenylyl cyclase system.

- 3492 ANALYSES OF BASES, OLIGONUCLEOTIDE FREQUENCIES, AND THE LABELING KINETICS OF HIGH MOLECULAR WEIGHT RNA FROM HUMAN LEUKEMIAS AND LYMPHOMAS. (Ger.) Seeber, S. (Clin. Polyclin. Internal Med., Essen, Germany) and C. G. Schmidt. *Verhandl Dtsch Ges Inn Med* 79:511-513, 1973.

The synthesis and primary structure of 45 S-RNA formed in the nucleolus, and its breakdown to ribosomal 18 S-RNA and 28 S-RNA in human acute myeloid leukemia and Burkitt's lymphoma were studied, on the basis of known morphological changes of the nucleolar apparatus in malignant cells. Following highly specific ^{32}P -labeling of the cells in vitro, and following ribosome and nucleus isolation, the specific activity of the nuclear 45 S-RNA fraction as a measure of the biochemical activity of the nucleolar apparatus, the specific activities of ribosomal 18 S-RNA and 28 S-RNA, the base composition of 45 S-RNA and 18 S/28 S-RNA- and the oligonucleotide distribution following complete digestion of the nucleic acids by pancreatic ribonuclease were used as parameters. Under comparable conditions, the specific activity of nuclear 45 S-RNA was found to be highest in Burkitt's lymphoma and leukemic lymphosarcoma, as well as in acute myeloid, and lymphatic leukemias. The labeling was weaker in chronic lymphatic leukemia, but more pronounced than in non-stimulated, normal lymphocytes. The activity of the nucleolar apparatus was found to be lowest in chronic myeloid leukemia cells. The breakdown of nucleolar 45 S-RNA to ribosomal 28 S-RNA and 18 S-RNA appears to be blocked in acute myeloid and lymphatic leukemias.

3493 DNA CONTENT OF MITOTIC CELLS IN CERVICAL DYSPLASIA AND CARCINOMA *IN SITU*. (Ger.)

Wagner, D. (Lutheran Deaconess Hosp., Freiburg/Breisgau, Germany). *Verh Dtsch Ges Pathol* 57:211-214, 1973.

Six patients with mild to serious intraepithelial cervical dysplasia and four with cervical carcinoma *in situ* were examined for the presence of tumor stem lines by using DNA Feulgen microspectrophotometry (Patau's two-wave-length method). All cases showed a wide range of DNA contents in metaphase or interphase nuclei with partially manifest "DNA stem lines" in the aneuploid range, as well as a smaller DNA content in the anaphase-telophase figures. The telophase values were in the diploid range and did not differ from the diploid distribution of lymphocyte controls in eight of ten cases. There was wide distribution, ranging from diploid to tetraploid, and no clear-cut stem line was discernible in two cases. These studies established the presence of stem lines in the majority of the cases of spontaneous human intraepithelial neoplasia, which in good agreement with literature findings in experimental tumor systems and in spontaneously occurring human tumors. The cells of the tumor stem lines had diploid or nearly diploid chromosome sets, i.e., cell proliferation originated in diploid cell lines. The aneuploid stem lines found in interphase and metaphase cells cannot be regarded as an expression of the formation of aneuploid tumor cell stems. Rather, aneuploid DNA stem lines result from blockade of the mitotic cell division of tumor cells with aneuploid chromosome sets in the metaphase. Thus, the aneuploid cell population, while giving the tumor its malignant character, is not a measure of the proliferation capacity of the tumor.

3494 DISTRIBUTION OF REPETITIVE AND NONREPETITIVE SEQUENCE TRANSCRIPTS IN HeLa AND mRNA.

(E.) Klein, W. H. (Div. Biol., California Inst. Technol., Pasadena), W. Murphy, G. Attardi, R. J. Britten and E. H. Davidson. *Proc Natl Acad Sci USA* 71(5):1785-1789, 1974.

Polyadenylated messenger RNA extracted from HeLa cells was hybridized with a mass excess of HeLa DNA. The kinetics of the hybridization reaction indicated that most of the messenger RNA was transcribed from nonrepetitive DNA. The amount of messenger RNA hybridized to the DNA was measured both with and without prior RNase treatment. Comparison of the results indicated that within the limits of detection, HeLa messenger RNA does not contain repetitive sequence elements covalently linked to nonrepetitive sequence transcripts. However, a small fraction of the HeLa messenger RNA preparation was transcribed entirely from repetitive DNA sequences. This fraction represented about 6% of the total polyadenylated messenger RNA preparation. It appears that at least part of the nontranslated messenger RNA must also be transcribed from single-copy DNA.

3495 ELECTROPHORETIC STUDIES OF RNA IN GASTRIC TUMORS AND THE GASTRIC MUCOSA IN HUMANS.

(Rus.) Kalinovskii, V. P. (N. N. Petrov Inst. Oncol., Leningrad, USSR), T. A. Goriukhina, and I. F. Seits. *Vopr Onkol* 20(12):39-44, 1974.

Electrophoretic studies of the main RNA fraction in malignant gastric tumors and the gastric mucosa were conducted on 34 patients with stomach cancer, 12 patients with peptic ulcer, and 6 with polyposis. Electrophoresis in 2.5% polyacrylamide gel showed the main fractions of cytoplasmic RNA were similar. Gastric tumors revealed slightly increased content of total and ribosomal RNA and a decrease content of transport RNA compared to the gastric mucosa.

3496 TRANSFER RNA METHYLASE ACTIVITY IN BENIGN HUMAN OVARIAN NEOPLASMS. (E.) Sheid, B. (State U. New York, Downstate Med. Ctr., Brooklyn), T. Lu and J. H. Nelson, Jr. *Cancer Res* 34(9):2416-2418, 1974.

Protein, RNase, and tRNA methylase activity were measured in human ovarian tissues obtained from 16 patients undergoing oophorectomies for various benign lesions. All of the benign tumors except one arrhenoblastoma showed the same range of tRNA methylase activity and tRNA-methylating capacity as did normal ovarian tissues. The values were independent of the type of tissue, stromal or epithelial, of which the tumor was composed. The arrhenoblastoma, a rare masculinizing tumor composed of Sertoli and Leydig cells is generally classified as benign, but it has a high potential for developing malignant characteristics unless removed immediately. The 5-fold increase in tRNA methylase activity in this tumor may indicate that it was in a premalignant state. Thus, tRNA methylase activity can be used to determine the pathological state of an ovarian neoplasm.

3497 ISOLATION AND PARTIAL CHARACTERIZATION OF THE MULTIPLE FORMS OF DEOXYRIBONUCLEIC ACID-DEPENDENT RIBONUCLEIC ACID POLYMERASE IN THE MOUSE MYELOMA MOPC 315. (E.) Schwartz, L. B. (Dept. Biol. Chem., Washington U., St. Louis, Mo.), V. E. F. Sklar, J. A. Jaehning, R. Weinmann and R. G. Roeder. *J Biol Chem* 249(18):5889-5897, 1974.

RNA polymerase was solubilized from whole cell homogenates of the mouse myeloma tumor, MOPC 315. Four forms of the solubilized enzyme were isolated by ion exchange chromatography; they were designated I, II, IIIA, and IIIB. The enzymes appear analogous to the Class I, II, III, RNA polymerases defined in other eukaryotic system. Ionic strength optima, metal ion effects, α -amanitin sensitivities, and relative activities with poly (d(A-T)) and calf thymus DNA templates are different for Class I, II, and III RNA polymerases, but are identical for IIIA and IIIB. When the amounts of the different enzymes were measured in subcellular fractions of myeloma cells, RNA polymerase I was found predominantly in the

nucleolar fraction, II and IIIA were found predominantly in the nucleoplasmic fraction, and IIIB was found predominantly in the cytoplasmic fraction. This latter enzyme may be of cytoplasmic origin. The cellular levels of the RNA polymerases were compared in MOPC 315 tissues and in normal tissues under various physiological conditions. The levels of enzymes I and II were increased in the myeloma tissue relative to calf thymus, mouse liver, and mouse spleen, and were increased in liver and spleen tissues from tumor-bearing mice and younger (6 wk) mice relative to tumor-free mice and older mice (10 wk), resp. The levels of enzyme II were less variable under these circumstances. The activities of the ribosomal RNA genes and the 4S and 5S RNA genes may be regulated by similar mechanisms operative at the level of enzymes I, IIIA, and IIIB. The levels of enzyme II alone probably cannot differentially regulate the rates of synthesis of specific gene products; additional components may direct enzyme specific and/or activity *in vivo*.

- 3498 INTRAGENOMAL DISTRIBUTION OF DNA REPAIR SYNTHESIS: REPAIR IN SATELLITE AND MAINBAND DNA IN CULTURED MOUSE CELLS. (E.) Lieberman, M. W. (Natl. Cancer Inst., Bethesda, Md.) and M. C. Poirier. *Proc Natl Acad Sci USA* 71(6):2461-2465, 1974.

DNA repair synthesis was examined in mouse satellite and mainband DNA derived from confluent BALB/c 3T3 cells damaged with UV radiation or N-acetoxy-2-acetylaminofluorene (NA-AAF). Two different approaches were used: contact-inhibited cells were treated with hydroxyurea to reduce replicative synthesis to low levels; and bromodeoxyuridine was used to label newly replicated DNA in cells which had escaped contact inhibition. The DNA was separated into mainband and satellite fractions in Ag^+ Cs_2SO_4 gradients. After treatment with either UV irradiation or NA-AAF, repair synthesis occurred to the same extent in the mainband and satellite fractions. Repair synthesis increased over a UV dose of 30-200 erg/mm^2 , the extent of repair in the two DNA species being similar at each dose level. Analysis of the separated strands of satellite DNA from the UV-irradiated cells indicated that the extent of repair is closely correlated with the availability of pyrimidines for cyclobutyl dimer formation and provided evidence that repair synthesis occurs at the site of damage. The data suggest that at least one group of highly repetitive, nontranslated DNA sequences is repaired to about the same extent as the rest of the genome.

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- 3505 HISTAMINE-HISTAMINASE-HISTIDINE DECARBOXYLASE-HISTAMINOPEXY SYSTEM IN ACUTE LEUKEMIAS. (Rus.) Timoshenko, L. I. (Kiev Sci. Res. Inst. Hematol. Blood Transfusion, USSR) and V. I. Klimenko. *Vrach Delo* (6):58-71, 1974.

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